Identification of factors in the natal and neonatal period influencing enamel development in the permanent first molars and incisors

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Dedications

My thesis is dedicated to……

Firstly, this thesis is dedicated to my beloved mother Mrs Wan Rubiah Wan Abdullah and beloved father Mr Abdul Halim Abdul Latiff whose words of encouragement and support never ends. Their unconditional love and support, always believing in me and encouraging me to be the best in everything I do. Thank you Mama and Ayah for believing in me, always encouraging me to chase my dream.

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My brothers Hazami and Zulfadli.

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My big family- Mr Jamaluddin and Mrs Leli, Shuhaida and Ammar and their children, Faeza and Shazli and their children, Fazly and Sarina and their sons.
Abstract

Molar-Incisor Hypomineralisation (MIH) is defined as hypomineralisation of one to four first permanent molars, frequently associated with affected permanent incisors. MIH refers to a qualitative enamel developmental defect of systemic origin clinically manifesting as demarcated discolouration that ranges from white-opaque to yellow-brown defects that are soft and fragile. The possible aetiology of MIH remains unclear and is thought to be acquired via multifactorial, systemic disturbances during amelogenesis. Some of the possible aetiologies that have been suggested to be associated with this condition are high fever, oxygen deficiency at birth, prenatal and perinatal sickness, respiratory infections in the first three years of life, or nephritic disease. MIH has also been suggested as being associated with toxins and antibiotic consumption, malnutrition, intestinal inflammation, diarrhoeas and hypoparathyroidism occurring during the critical period of enamel development.

The overall aim of the current study was to better understand the clinical features of MIH and to contribute to the knowledge of the aetiology of MIH. The specific objectives were to assess relationships of pregnancy, delivery history and birth complications in mothers of children identified with and without MIH.

A matched case-control study was designed to further investigate and help to identify factors from perinatal and postnatal time periods that could influence enamel development in the first permanent molars and incisors related to MIH, through the assessment of medical birth records. The case group comprised of children who had been diagnosed with MIH selected from Paediatric Dentistry records at the University of Otago School of Dentistry. The control group was either volunteered by the case group or randomly selected from the Dental Therapy Clinic at the School of Dentistry. All study children received a clinical
assessment that recorded developmental defects of enamel (DDE) and dental caries status. Mothers of these children completed questionnaires to record pregnancy history, delivery history and the child’s medical history in the first years of life after birth. Mothers’ and children’s medical birth records were assessed for further pregnancy and delivery history. Univariate and bivariate statistics were computed using SPSS version 19.0 and STATA version 10. The level of significance was set at P<0.05.

The case group had similar sociodemographic characteristics to the control group. Statistically there was no significant difference in the ethnic variation between the case and the control groups. The prevalence of MIH defects were found to be higher in the first permanent molars than in the incisors. The prevalence of MIH defects was similar in the maxillary first permanent molars and mandibular first permanent molars, but were found to be higher in tooth 26 (93.5%), although this difference was not statistically significant. MIH defects were more common in the maxillary incisors than in the mandibular incisors. Children with MIH were diagnosed to have a higher overall caries experience in the deciduous and permanent dentitions than children without MIH. Children diagnosed with MIH had more medical problems related to birth, such as oxygen deprivation, one or more signs of foetal distress, premature births, low birth weight (LBW) and were born through assisted delivery. Mothers of children diagnosed with MIH had received more drugs such as nitrous oxide, pethidine and antibiotic(s) during delivery. No associations were found between the occurrence of MIH and medication(s) taken by mothers during pregnancy or medical problems during pregnancy.

The findings from the current study do have clinical implications with higher number of medical problems related to birth having been demonstrated as an indicator for an increased prevalence of MIH.
Preface

The thesis is divided into six chapters.

The first chapter provides the introduction, objectives and outline to the current study.

The second chapter reviews the literature surrounding dental development and developmental defects of dental enamel, Molar-Incisor Hypomineralisation (MIH), MIH prevalence, MIH characteristics and features, clinical presentation, diagnosis and management of MIH and possible aetiologies in the occurrence of MIH.

The third chapter has two sections, with the first detailing the background to the methodology and the second section describing the methodology used to investigate the factors in the natal and neonatal period influencing enamel development in the permanent first molars and incisors.

The fourth chapter presents the results on the assessed oral factors with respect to the group and sociodemographic characteristics, and the associations between the oral and factors in the natal and neonatal period.

The fifth chapter discusses the findings with reference to previous research internationally and nationally.

Chapter six draws conclusions and suggests future research directions.

The complete data collected for this research has not been included due to its significant volume.
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<th>Description</th>
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<tr>
<td>ABIS</td>
<td>All Babies in Southeast Sweden</td>
</tr>
<tr>
<td>AI</td>
<td>Amelogenesis imperfecta</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APECED</td>
<td>Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy</td>
</tr>
<tr>
<td>APS-C</td>
<td>Advanced Photo System type-C (APS-C)</td>
</tr>
<tr>
<td>C</td>
<td>Carbon</td>
</tr>
<tr>
<td>Ca</td>
<td>Calcium</td>
</tr>
<tr>
<td>COHS</td>
<td>Community Oral Health Service</td>
</tr>
<tr>
<td>CPP-ACP</td>
<td>Casein phosphopeptide-amorphous calcium phosphate</td>
</tr>
<tr>
<td>DDE</td>
<td>Developmental defects of enamel</td>
</tr>
<tr>
<td>DIFOTI</td>
<td>Digital imaging fibre-optic transillumination</td>
</tr>
<tr>
<td>DMFS</td>
<td>Decayed, missing, filled, surfaces in permanent dentition</td>
</tr>
<tr>
<td>dmfs</td>
<td>Decayed, missing, filled, surfaces in primary dentition</td>
</tr>
<tr>
<td>DMFT</td>
<td>Decayed, missing, filled, tooth in permanent dentition</td>
</tr>
<tr>
<td>DMH</td>
<td>Deciduous molar hypomineralisation</td>
</tr>
<tr>
<td>DSLR</td>
<td>Digital single-lens reflex</td>
</tr>
<tr>
<td>EAPD</td>
<td>European Academy of Paediatric Dentistry</td>
</tr>
<tr>
<td>ECM</td>
<td>Electrical conductance measurements</td>
</tr>
<tr>
<td>EDJ</td>
<td>Enamel-dentine-junction</td>
</tr>
<tr>
<td>FDI</td>
<td>Federation Dentaire Internationale</td>
</tr>
<tr>
<td>FPM</td>
<td>First permanent molar</td>
</tr>
<tr>
<td>GA</td>
<td>General anaesthesia</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GIC</td>
<td>Glass ionomer cement</td>
</tr>
<tr>
<td>HFM</td>
<td>Hand, foot and mouth</td>
</tr>
<tr>
<td>ICDAS</td>
<td>International Caries Detection and Assessment System</td>
</tr>
<tr>
<td>ICW-CCT</td>
<td>International Consensus Workshop on Caries Clinical Trial</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared laser fluorescence</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>MIH</td>
<td>Molar-incisor hypomineralisation</td>
</tr>
<tr>
<td>NaOCL</td>
<td>Sodium hypochlorite</td>
</tr>
<tr>
<td>NEAC</td>
<td>National Advisory Committee on Health and Disability Support Services Ethics</td>
</tr>
<tr>
<td>P</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>PCB</td>
<td>Polychlorinated biphenyls</td>
</tr>
<tr>
<td>PEB</td>
<td>Post-eruptive breakdown</td>
</tr>
<tr>
<td>QLF</td>
<td>Quantitative laser or light fluorescence</td>
</tr>
<tr>
<td>RAG</td>
<td>Research Advisory Group</td>
</tr>
<tr>
<td>RAH</td>
<td>Rohaida Abdul Halim</td>
</tr>
<tr>
<td>sd</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-economic-status</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SSC</td>
<td>Stainless steel crown</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WMT</td>
<td>W Murray Thomson</td>
</tr>
</tbody>
</table>
Chapter I. Introduction, objectives and outline

Introduction

Developmental dental anomalies are common in both deciduous and permanent dentitions and can affect enamel and/or dentine. Distinguishing normal dental development from development that has pathological changes requires careful evaluation of the patient including full prenatal, neonatal and postnatal medical histories, family histories, clinical and radiographic examination, and histology where appropriate. Developmental anomalies of teeth are defined as deviations from the normal including in colour, shape, size, tissue quality or number. Systemic as well as local factors may contribute to these developmental disturbances. Developmental dental anomalies may present multiple or complex problems when they affect form and function. Anterior teeth anomalies may have a significant psychological impact. They usually present in the primary or early mixed dentitions and often require both immediate management and longer-term management through the development of the permanent dentition. This may include multi-disciplinary care following the diagnosis, and long-term treatment plan.

Developmental defects of enamel (DDE) are commonly encountered in clinical practice. DDE often result from disturbances to the highly specialised ameloblasts cells at vulnerable stages of amelogenesis. The process of enamel formation occurs over a long period of time, and once formed, enamel does not undergo the remodelling process. Any disturbances during development can manifest as permanent defects in the erupted tooth (Suckling, 1989).

Classically, attention on developmental defects of enamel was centered around the rare genetic disorder amelogenesis imperfecta (AI) and on dental fluorosis, a widespread developmental defect of enamel acquired from
excessive fluoride intake. Over the past decade, the acquired developmental
defect termed Molar-Incisor Hypomineralisation (MIH) (Weerheijm, 2003) has
been encountered in clinical practice with reported prevalence of between 2.8
percent (Cho et al., 2008) and 40.2 percent (Soviero et al., 2009) worldwide
and 18.8 percent in New Zealand (Mahoney and Morrison, 2011). MIH refers
to a qualitative enamel developmental defect of systemic origin that affects the
first permanent molars and occasionally the incisors. Clinically, this manifest
as demarcated discolouration that range from white-opaque to yellow-brown
defects that are soft and fragile.

Currently, the aetiology of MIH remains unclear and is thought to be
acquired via multifactorial, systemic disturbances during amelogenesis
(Alaluusua, 2010, Crombie et al., 2009, Whatling and Fearne, 2008, Fagrell,
2011, Weerheijm, 2004). Some of the possible aetiologies that have been
suggested to be associated with this condition are high fever, oxygen
deficiency at birth, prenatal and perinatal sickness, respiratory infections in the
first three years of life, or nephritic diseases. MIH has also been suggested as
being associated with toxins and antibiotic consumption, malnutrition,
intestinal inflammation, diarrhoeas and hypoparathyroidism occurring during
the same crucial period. Fearne et al (Fearne et al., 2004) suggested that the
disturbances could be more chronic in nature over a longer period, based on the
random distribution of hypomineralisation in the affected teeth. A family
history of enamel defects is commonly reported for MIH, but the association
has not been shown to be statistically significant (Whatling and Fearne, 2008).
The soft-fragile MIH-affected enamel, resulted in high failure rates of
restorative treatment (Jälevik and Klingberg, 2002, Mejare et al., 2005). There
is little knowledge and understanding of the structure and biochemistry of MIH
enamel and their link to its biomechanics, adding to the complexity in
management of this developmental disease. Therefore, by understanding its
causes and aetiology, it is reasonable to anticipate that MIH may be managed
better in the future.
**Aims and objectives**

The overall purpose of this study was to better understand the clinical features of MIH and contribute to the knowledge about the aetiology of MIH.

The aims of the study were:

- To investigate factors in the perinatal and early childhood periods that may be associated with the development of molar incisor hypomineralisation.
- To determine if all cases of MIH present with common factors or there are a range of associated factors which occur at different times in tooth development.

The specific objectives were:

- To investigate pregnancy, delivery history and birth complications in mothers of children identified with and without MIH, through structured interviews and review of the children’s and mother’s birth records.
- To record birth weight, gestational age, infant stress during delivery, early childhood illnesses, allergies, immunization history, breastfeeding history, antibiotic and other drug use during the first four years of life for children with and without MIH.

**Significance of the research**

Children with MIH are at higher risk of having significant sensitivity and early loss of permanent teeth due to the complex restorative care required throughout life or due to early infection of these teeth because of bacterial leakage through the exposed dentine.
Further understanding of the aetiology of this condition may provide the ability to predict children at risk allowing early intervention to improve enamel development before eruption, protect affected teeth as they erupt, and possibly to avoid or decrease exposure to certain factors during enamel formation.

**Study outline**

After obtaining ethical approval, identified children aged 6 to 12 years who had been diagnosed with MIH and children without MIH were invited to participate in the study. They underwent a clinical examination, their mother answered several health questionnaires, and the participants’ medical records were assessed.

The following chapters provide, a summarised critical review of the published literature on MIH enamel, followed by a brief background and theoretical description of the materials and methods used in this study. The results chapter presents the findings of the study, while a final discussion and conclusion chapter will conclude the thesis, linking the different results together and suggesting possible future investigations.
Chapter II. Review of the literature

**Introduction and definition**

Developmental defects of enamel are not uncommon; they can be seen both in the primary and permanent dentitions. The defects can be divided into hypomineralisation and hypoplasia (Jälevik and Norén, 2000, Beentjes et al., 2002). Enamel hypoplasia is defined as a quantitative defect of the enamel and is characterised by deficiency in tooth substance that ranges from minor pits and grooves to total absence of enamel caused by disruption to the ameloblasts during matrix secretion (Suckling, 1989). On the other hand, enamel hypomineralisation is defined as a qualitative defect of the enamel caused by disruption that occurs during either the calcification or maturation phase of enamel formation. This usually causes the affected tooth or teeth to appear opaque. Both of the terms are based on descriptive criteria with no association to the aetiology (Clarkson and O'Mullane, 1989, Clarkson, 1989). In some cases, both hypoplasia and hypomineralisation exist together and it may be difficult to differentiate between true hypoplasia and posteruptive breakdown of hypomineralised enamel (Fearne et al., 2004).

**Dental development**

Dental development (morphologically as well as molecularly) closely resembles the development of other epithelial appendages such as hair follicles, mammary glands and kidneys. Interactions between the ectoderm and underlying mesenchyme constitute a central mechanism regulating the morphogenesis of all of these organs. The only difference between dental development and the development of other epithelial appendages is in the formation of the hard tissues; ectomesenchymal-derived dentine and
epithelium-derived enamel. This is a characteristic feature of dental development.

Teeth develop as a result of sequential and reciprocal epithelial-mesenchymal interactions between the ectodermal and mesenchymal tissues. During this process, the simple oral ectoderm thickens, buds, grows and folds to form the complex shape of the tooth (Thesleff, 2003).

In human beings, dental development and mineralisation commences before birth and this process continues into adolescence, when the permanent molars complete their mineralisation. The first sign of tooth mineralisation is seen in the primary lower incisors at the beginning of the second trimester of pregnancy, and it is completed around three months after birth. First permanent molars are the first permanent teeth to mineralise (Table 2.1), a process that begins around birth and is completed at approximately at three and a half to four years of age (Reid and Dean, 2006). Hence, any developmental defects of enamel in the first permanent molars may be related to any disturbances within that period.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Calcification begins</th>
<th>Crown completed</th>
<th>Eruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>3 months</td>
<td>4 ½ years</td>
<td>7 ¼ year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 ½ years</td>
<td>6 ¼ year</td>
</tr>
<tr>
<td>Lateral</td>
<td>11 months</td>
<td>5 ½ years</td>
<td>8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 years</td>
<td>7 ½ years</td>
</tr>
<tr>
<td>1st Molar</td>
<td>32 weeks in utero</td>
<td>4 ½ years</td>
<td>6 ¼ years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 ¼ years</td>
<td>6 years</td>
</tr>
</tbody>
</table>

Table 2.1. Chronology of tooth development of permanent molars and incisors as described by Proffit (Proffit et al., 2007)
Dental enamel

Dental enamel is a unique tissue, being a highly mineralised tissue of ectodermal origin, formed by cells called ameloblasts (Nanci, 2008). They are derived from the internal enamel epithelium of the enamel organ. Dental enamel is the hardest tissue in the body, characterised by rhythmic appearances that are preserved within the tissues short and long period lines of incremental growth (Simmer et al., 2010). Growth lines that form during tooth development are permanent as dental enamel and dentine are remodelled by cycles of resorption and deposition. There are two regularly occurring incremental markers in dental enamel: daily cross-striation and long period of striae of Retzius which correspond to what was the enamel surface at precise points in time during the secretory stage of amelogenesis (Reid and Ferrell, 2006). As dental enamel is characterised by a lack of metabolic activity once formed, any disturbances during development can manifest as permanent defects in the erupted tooth.

Mature enamel is highly mineralised, consisting of 96% mineral and 4% organic material and water. The mineral content of enamel is predominantly hydroxyapatite and the organic content contains proteins, lipids and water. Hydroxyapatite crystallites form enamel rods, or formerly known as enamel prisms. Because the final step of epithelial-mesenchymal interactions instructing early tooth development, enamel formation or amelogenesis by ameloblasts begin only after mineralisation of predentin has started.

Amelogenesis can be divided into three distinct stages of the ameloblast life cycle: (1) matrix formation (or the secretory stage), (2) initial mineralisation (or transition stage); and (3) final maturation (Suga, 1989). At the secretory stage, large amounts of enamel matrix proteins are secreted by ameloblasts. Enamel formation is first initiated on the dentine horn, where the first epithelial cells differentiate into pre-ameloblasts and form a thin layer of aprismatic enamel on the dentine surface (Simmer et al., 2010). This
differentiation process is driven by signals coming from the enamel knot and the underlying odontoblasts (Simmer et al., 2010). Enamel matrix is then laid down in the extracellular space along the ameloblast (distal) cell membrane, and it is associated with the secretion of enamel matrix proteins (amelogenin, ameloblastin, enamelin) and enamelysin, a proteolytic enzyme that cleaves enamel matrix proteins (Fincham et al., 1999). These enamel proteins form a mineralisation front and induce the simultaneous production of thousands of enamel ribbons near the plasma membrane of each ameloblast. As ameloblasts secrete enamel proteins, they retreat from the existing enamel surface, increasing the thickness of enamel extracellular space. As enamel matrix is laid down, the inner two-thirds of the matrix is only slightly mineralised, except for the narrow innermost layer it is slightly more highly mineralised than the outer one-third.

Once the full thickness of enamel has been deposited, the secretory ameloblasts transform through a short transitional phase into maturation stage ameloblasts. These ameloblasts are responsible for enamel matrix degradation accompanied by intensive mineralisation of the enamel as preexisting hydroxyapatite crystals grow in width and thickness (Simmer et al., 2010). When the maturation stage commences, secondary mineralisation takes place first, from the surface towards the inner layer. As secondary mineralisation reaches the innermost layer, a tertiary mineralisation begins to progress from the outer side of the innermost layer toward the enamel surface. The narrow outer layer mineralises very slowly during the middle and late stages of maturation, but it finally achieves the highest mineralisation of the entire enamel layer (Suga, 1989). The very narrow innermost layer mineralises slowly without expanding its width.

The maturation phase involves an increase in mineral content and the removal of organic material, especially amelogenins and enamelin proteins. The mature ameloblasts regulate the final mineralisation of enamel. The
enamel layer hardens as the crystallites increase growth in width and thickness, resulting in mineralised tissue containing more than 95% mineral by weight. Some of this maturation occurs after eruption of the tooth into the mouth. Although these processes are relatively well understood, the aetiology of developmental defects of enamel remains ambiguous because the structure and chemical composition of dental enamel are so complex and difficult to study.

**Developmental defects of dental enamel**

**Background and clinical aspects**

Because dental formation and development is strictly genetically controlled, disturbances in the development may be attributed to genetic or environmental causes, especially at the early stage of maturation, because the ameloblasts are highly sensitive to environmental disturbances (Suga, 1989).

Once enamel is formed, it does not undergo any remodelling processes. Therefore, the effects of any insults on ameloblasts are permanent and irreversible, and are detectable as defects in the mature enamel. However, the majority of these defects are idiopathic and environmental disturbances can further be categorised as systemic or local. In general, disturbances in the initial matrix secretion phase of amelogenesis will most likely present as morphologic defects termed enamel hypoplasia (Suckling, 1989, Suckling and Pearce, 1984), usually caused by restriction of crystal elongation which results in pathologically thin enamel. The teeth are characterised by a deficiency of tooth substance ranging from minor pits and grooves to the total absence of enamel. Disturbances during the mineralisation/calcification or maturation phases produce morphologically normal but structurally defective enamel, or pathologically soft (hypomineralisation/hypomaturation) enamel of normal
thickness. The teeth will appear mottled and the enamel will have a qualitative defect (Suckling and Pearce, 1984) termed enamel hypomineralisation (Weerheijm et al., 2001b). This is because, in hypomineralised enamel, the enamel is more porous and visible light is reflected poorly. Generally, normal enamel in permanent teeth is translucent to visible light, which passes through the enamel and is reflected at the enamel-dentine junction. Examples of enamel defects are shown in Table 2.2.

The cusp tips of first permanent molars start developing in the fourth month of gestation, and the four cusps become united at around the age of six months postnatally. According to Reid and Dean (Reid and Dean, 2006), enamel formation as a whole takes approximately one thousand days and two-thirds of this is devoted to the maturation stage of amelogenesis. Previous research suggested that the most critical period for enamel defects in the first permanent molars and incisors is the first year of life coinciding with early maturation (Suga, 1989). However, because enamel maturation in the first permanent molars takes several years (later maturation stage), some hypomineralisations may occur later.

Disturbances in enamel mineralisation may appear clinically as opaque areas with loss of translucency, with colours ranging from white to yellowish-brown, or as areas of defects where mineralisation was disrupted. The timing of disturbance(s) of enamel may not be possible to determine, even when the defects are related to the timing of development. The extent of tissue defects is not always able to be evaluated clinically, leading to difficulty in assessing the length of time of disturbance(s) accurately. Sometimes, appropriate information can be found with histological analyses. However, this is a drastic step to take because it requires tooth extraction.

Knowledge of the aetiology of hereditary dentine and enamel defects in mice and humans may help reveal mechanisms of impaired dental hard tissue
formation caused by environmental toxicants. *In vitro* animal studies on the effects of environmental toxicants on developing teeth can increase the understanding of mechanisms of aberrant human tooth development, especially those due to environmental factors. Furthermore, experimental animal studies may help assess human risk for developmental dental disturbances with an environmental background.

**Hereditary enamel defects**

*Amelogenesis imperfecta (AI)*. Amelogenesis imperfecta (AI) is a term for a clinically and genetically heterogeneous group of conditions affecting the dental enamel, occasionally in conjunction with other dental, oral or extraoral tissues. AI represents a group of developmental conditions, genomic in origin, which affect the structure and clinical appearance of enamel of all (or nearly all) the teeth in a more or less equal manner, and may be associated with morphologic or biochemical changes elsewhere in the body (Crawford et al., 2007). Diagnosis of AI involves exclusion of extrinsic environmental or other factors, establishment of a likely inheritance pattern, recognition of phenotype, and correlation with the dates of tooth formation to exclude chronological developmental disturbances. Its prevalence varies from 1 in 700 to 1 in 14,000 (Crawford et al., 2007), according to the populations studied. The enamel may be hypoplastic, hypomineralised or both and affected teeth may be discoloured, sensitive or prone to disintegration. AI may exist in isolation or be associated with other abnormalities as part of a syndrome. It may show autosomal dominant, autosomal recessive, sex-linked and sporadic inheritance patterns. AI can be classified based on the phenotype (appearance) exclusively, or by phenotype as the primary discriminant and the mode of inheritance as a secondary factor in diagnosis (Crawford et al., 2007).

Enamel defects are also associated with various syndromes and diseases. For example, the phenotypes of tricho-dento-osseous syndrome, vitamin D-dependent and vitamin D-resistant rickets, and autoimmune
polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) involve enamel hypoplasia (Bailleul-Forestier et al., 2008). Patients with coeliac disease may present with enamel defects ranging from defects in colour to severe hypoplasia, and patients with epidermolysis bullosa may present with variable degrees of hypoplasia (Wright et al., 1993).

*Developmental defects of enamel caused by environmental factors*

Developing enamel is highly susceptible to hypomineralisation defects of environmental origin at the transitional and early maturation stages of amelogenesis (Suga, 1989). A well known specific type of enamel hypomineralisation is fluorosis, caused by excessive intake of fluoride during these stages. At low doses, fluoride is the most important caries-preventive agent in dentistry. Other environmental organic toxicants, such as polychlorinated dibenzo-p-dioxins and dibenzofurans, have also been linked with enamel defects in human enamel (Alaluusua and Lukinmaa, 2006) but these studies were later discounted by Laisi et al (Laisi et al., 2008) and Kuscu et al (Kuscu et al., 2009). Their study found no association between molar-incisor hypomineralisation (MIH) and the level of exposure to dioxins.

The stage of dentition development is dependent on the age of the child and, therefore, the susceptibility of different teeth to developmental disturbances at different times varies (Suga, 1989). The development of the first permanent molars and incisors begins in the fourth month of gestation and their mineralisation starts around or soon after birth; it completes at the end of fifth year of life for upper incisors and at about three years for molars (Reid and Dean, 2006). At around the same time as the development of permanent first molars and permanent incisors, the development of second primary molars begins, but the maturation of the permanent teeth occurs more slowly (Butler, 1967, Proffit et al., 2007). This puts the permanent incisors and first permanent molars at a greater risk for defects caused by systemic environmental factors in
the first five years of life. If any disturbance or risk factor occurs during the overlapping period of development of both dentitions, enamel defect may occur in the primary as well as in the permanent teeth (Aine et al., 2000).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Enamel hypomineralisation</th>
<th>Enamel hypoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of defect</td>
<td>Qualitative</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Clinical</td>
<td>Demarcated opacities of</td>
<td>Partial or total</td>
</tr>
<tr>
<td>characteristic</td>
<td>white to yellowish-brown</td>
<td>absence of enamel</td>
</tr>
<tr>
<td></td>
<td>discolouration</td>
<td>Pits, horizontal</td>
</tr>
<tr>
<td></td>
<td>Normal thickness of enamel</td>
<td>or vertical</td>
</tr>
<tr>
<td></td>
<td>Enamel is soft, porous and</td>
<td>grooves</td>
</tr>
<tr>
<td></td>
<td>poorly differentiated from</td>
<td>Edges with adjacent</td>
</tr>
<tr>
<td></td>
<td>normal tooth tissue</td>
<td>normal enamel are</td>
</tr>
<tr>
<td></td>
<td>Post-eruptive breakdown</td>
<td>smooth</td>
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<tr>
<td></td>
<td>may occur in molars</td>
<td>Symmetrical or</td>
</tr>
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<td></td>
<td>Asymmetrical opacities</td>
<td>isolated lesion</td>
</tr>
<tr>
<td>Clinical</td>
<td>Asymmetrical demarcated</td>
<td>Diffuse opacity</td>
</tr>
<tr>
<td>appearance</td>
<td>opacity in incisors</td>
<td>in incisors</td>
</tr>
<tr>
<td></td>
<td>Asymmetrical enamel</td>
<td>Hypoplasia of</td>
</tr>
<tr>
<td></td>
<td>opacities in upper first</td>
<td>upper and lower</td>
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<td></td>
<td>permanent molars with</td>
<td>incisors</td>
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<tr>
<td></td>
<td>posteruptive breakdown</td>
<td></td>
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<tr>
<td></td>
<td>Demarcated opacities of</td>
<td>Isolated demarcated</td>
</tr>
<tr>
<td></td>
<td>yellowish-brown discolouration</td>
<td>opacity in lower</td>
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<tr>
<td></td>
<td></td>
<td>right central</td>
</tr>
<tr>
<td></td>
<td></td>
<td>incisor</td>
</tr>
<tr>
<td>Possible</td>
<td>Remains obscure</td>
<td>Some hypoplastic</td>
</tr>
<tr>
<td>aetiological</td>
<td></td>
<td>defects are</td>
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<td>factors</td>
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<td>related to</td>
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<td></td>
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<td>condition</td>
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<td>Identifiable</td>
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<td></td>
<td></td>
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<td>insult (trauma or</td>
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<td></td>
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<td>local infection</td>
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<tr>
<td></td>
<td></td>
<td>of primary teeth</td>
</tr>
</tbody>
</table>

**Table 2.2.** Differences between two developmental defects of enamel according to FDI Commission on Oral Health, Research and Epidemiology (1982)(adapted from (dos Santos and Maia, 2012))
Molar-Incisor Hypomineralisation (MIH)

Background and definition

Over past decades, developmental defects of enamel in first permanent molars have had several labels: hypomineralised first permanent molars; idiopathic enamel hypomineralisation; non-fluoride hypomineralisation; cheese molars; and demarcated opacities of the first permanent molars (Weerheijm et al., 2001b). It was not until 2001 that the term Molar-Incisor Hypomineralisation was introduced by Weerheijm et al to describe the clinical presence of a qualitative enamel developmental defect of systemic origin that affects the first permanent molars and occasionally the incisors. Weerheijm et al (2001) defined Molar-Incisor Hypomineralisation (MIH) as a hypomineralisation of systemic origin of one to four permanent first molars, frequently associated with affected permanent incisors (Weerheijm et al., 2001b). This definition is now widely used and has been adapted by researchers and clinicians to describe MIH. However, based on the definition alone, it is not always possible to classify all affected first permanent molars as MIH. Hypomineralisation may not be related to MIH. An example is the diffuse opacities found in fluorotic enamel.

In 2003, unified judging criteria for the diagnosis of MIH were introduced by Weerheijm et al (Weerheijm et al., 2003). The criteria consisted of the presence of demarcated opacities evident in the change of the translucency/colour of the enamel, post-eruptive enamel breakdown (not hypoplasia), atypical restorations in terms of being different from typical caries-related restorations by occupying unusual surfaces and areas, extracted molars not due to caries, and failure of eruption of a molar or incisor.
Characteristics of MIH affected teeth

Based on the above mentioned judgement criteria and description of the defects in the literature, MIH enamel can be described as:

- A qualitative defective enamel classified as hypomineralised type that follows incremental lines of enamel formation, from cuspal to cemento-enamel junction (Farah et al., 2010a, Fearne et al., 1994).
- Well-demarcated defects with borders between defective enamel and sound enamel being usually distinct (Weerheijm, 2004).
- It can have different clinical presentations of enamel defects ranging from chalky white-opaque lesions with loss of translucency, or yellow, or brown, atypical restorations, and/or post-eruptive breakdown (Weerheijm, 2004).
- The cervical enamel of affected tooth or teeth is almost always sound with no evidence of defective structure (Farah et al., 2010c).
- Moving from the cervical level towards a more occlusal level, the defect is confined to the inner enamel while the outer enamel does not appear to be affected. The hypomineralisation lesions become more evident towards the occlusal and eventually spreading to the entire thickness of the enamel (Farah et al., 2010a).
- The cusp tips of MIH-affected teeth do not usually appear to be hypomineralised, but if a marginal ridge is involved, maximum height of the cusp tips seems to be affected (Farah et al., 2010a).
- The most severely affected teeth are the first permanent molars. The incisors are frequently affected, but not as severely as the molars (Lygidakis et al., 2008). There are also a few reports of the tips of permanent canines being affected as well as the second primary molars (Weerheijm, 2003, Elfrink et al., 2008).
- The distribution of the enamel defects in the mouth is usually asymmetrical; meaning that not all first permanent molars are necessarily affected to the same degree (Weerheijm, 2004).
In the absence of dental caries, the laser fluorescence of enamel as measured by DIAGNOdent (KaVo, Biberach, Germany) has been shown to indicate the degree of hypomineralisation in one study (Farah et al., 2008).

Enamel hypoplasia, the result of disturbance of ameloblast function during the secretory stage, is different from the post-eruptive breakdown characteristic of the more severe form of MIH. The borders between sound and hypoplastic enamel are smooth, while, in post-eruptive breakdown, the borders are irregular (Weerheijm, 2003). However, this is not easy to differentiate clinically and confusion between hypoplasia and post-eruptive breakdown may be expected.

MIH distribution varies among patients and also within a patient. Some studies have found no differences in severity between upper and lower molars (Chawla et al., 2008a, Cho et al., 2008, Jälevik et al., 2001a, Jasulaityte et al., 2008, Weerheijm et al., 2001a). In contrast, other studies have reported more maxillary molars affected than mandibular molars (Arrow, 2008, Leppaniemi et al., 2001, Lygidakis et al., 2008, Preusser et al., 2007).

Amelogenesis and MIH

In MIH-affected teeth, the defects are not hypoplastic because there is no discernable reduction in enamel thickness (Farah et al., 2010a, Fearne et al., 2004). This suggests that any reduction in enamel thickness seen clinically is an indication of post-eruptive disintegration of enamel. Furthermore, this clarifies that whatever disturbance affects the developing enamel happens after enamel secretion is complete and affects the transition and maturation phase of the mineralisation process in localised areas of enamel (Farah et al., 2010a).
Histological, chemical and mechanical features of MIH

The degree of porosity of the hypomineralised opaque areas varies from one tooth to another. In molars, the severely affected enamel is susceptible to rapid breakdown shortly after eruption into the oral cavity (Weerheijm et al., 2001b, Weerheijm, 2003). Breakdown occurs under masticatory forces, exposing dentine. The exposed dentine may be extremely sensitive, and this may cause the child to avoid brushing; it can also make the tooth vulnerable to rapid caries progression (Weerheijm, 2003, Weerheijm, 2004). In a study comparing the clinical and histological appearance of MIH enamel with normal enamel, polarisation microscope analyses showed yellow/brown enamel opacities to be more porous than lighter-coloured opacities (da Costa-Silva et al., 2011).

Jälevik and Noren (2000) reported that the affected enamel showed hypomineralisation localised to the cuspal region, with the cervical third of the enamel having a normal morphological and histological appearance. As reported by Xie et al (2008), microanalysis of sound and hypomineralised enamel showed two marked difference in the microstructure of MIH enamel: a less dense prism structure, with loosely packed hydroxyapatite crystals and wider sheath regions (Xie et al., 2008), especially in the porous part. These changes were suggested to occur during enamel maturation and may be responsible for the markedly lower hardness and elastic modulus of the affected enamel (Fagrell et al., 2010).

In addition, there are notable differences in the prism sheath of the enamel in the transitional region adjacent to demarcated defects in MIH enamel (Chan et al., 2010). Despite the translucent, normal appearance under transmission electron microscopy, the prism sheaths of enamel in the transitional region between the affected and unaffected MIH enamel are less mineralised and have been found to be weaker, which compromised its overall mechanical properties (Chan et al., 2010). The reason for this is still unclear, but it may be also related to the lack of organisation of enamel crystals due to
poorly demarcated prism boundaries in the affected regions (Mahoney et al., 2004) and seemingly loosely packed and less organised hydroxyapatite crystals in the affected enamel. The borders of the enamel rods were found to be indistinct and the inter-rod zones were hardly visible, or there were very thin rods with wide inter-rod zones (Jälevik et al., 2005). They speculated that poor acid solubility (after etching with 30% phosphoric acid for 30 seconds) could be due to the higher content of organic matter in the hypomineralised enamel. Robinson et al (Robinson et al., 1971) also have suggested that protein might reduce the access of inorganic ions to the crystallite surfaces in enamel.

The mineral composition of MIH enamel has been reported to be low (Jälevik et al., 2001c); on average, the mineral density is about 19% lower than in sound enamel (Baroni and Marchionni, 2011, Farah et al., 2010a, Jälevik and Norén, 2000). The Calcium:Phosphorus (Ca:P) ratio in MIH enamel (Jälevik et al., 2001c) related to a higher content of carbon (Fearne et al., 2004). Jalevik et al (2001) reported the mean Ca:P (1.4) was found to be lower in MIH enamel than in adjacent normal enamel (1.8). The fluoride content has been shown to be highly variable, the sodium content is higher towards the surface of the hypomineralised enamel, higher magnesium and potassium content and a negligible difference in the chlorine and strontium content. Fearne et al (2004), found that the high to low mineral concentration gradient from the enamel-dentine junction (EDJ) to the subsurface of MIH enamel is the opposite to what is seen in normal enamel. They suggested that this could possibly be related to the second phase of maturation being progressively more disturbed (Fearne et al., 2004).

MIH enamel was also reported to have a substantially higher protein content than the normal enamel, but close to a normal level of amelogenins. This characteristic distinguishes MIH from the hypomaturation defects containing high residual amelogenins, such as amelogenesis imperfecta or fluorosis (Mangum et al., 2010, Wright et al., 1996).
Clinical presentation and diagnosis of MIH

Clinically, MIH defects can be distinguished from carious lesions by their location on teeth, and their colour, shape and hardness. When posteruptive breakdown occurs, they appear different to hypoplastic defects, because in hypoplasia the borders between sound and hypoplastic enamel are smooth, while, in PEB the borders are irregular (Farah et al., 2010a, Fearne et al., 2004, Weerheijm, 2004). The MIH defect is a demarcated enamel defect on the occlusal, lingual/palatal and buccal surfaces of the crowns. It may affect one to all four permanent molars, and the presentation varies from individual to individual. The defects vary in colour, ranging from mild white or yellow opacities, to severe brown stained enamel.

MIH molars exhibit normal morphology and appearance except for differences in colour in the affected area(s), which range from opaque-white, to creamy yellow, to brown as shown in Figure 2.1. Areas of disintegrated enamel are close to the darkly stained enamel (Farah et al., 2010c). The lucency and smoothness of the affected areas are similar to normal enamel, except in the white-opaque areas, where the enamel appears dull.

Figure 2.1. Clinical images of MIH-affected teeth. The lower left molar shows a yellowish brown opacity (yellow arrow) with post-eruptive breakdown and the upper left molar shows a yellow opacity (blue arrow).
Farah et al (Farah et al., 2010c) reported that MIH enamel is more mineralised in the cervical region than it is midway between the cementoenamel junction and the occlusal surface. The thickness of enamel in the affected areas of MIH enamel was not less than in sound enamel. In the defective areas of MIH teeth, the cervical part was found to be less affected than the occlusal part. However, the defects usually did not involve the cusp tips. Therefore, MIH teeth do not appear to exhibit any discernible amount of reduction in enamel thickness. Any reduction in enamel thickness seen clinically in MIH teeth is an indication of post-eruptive breakdown. Farah et al (2010) suggested that enamel defects in MIH are hypomineralised defects of different severity that resemble the direction of the natural incremental lines of enamel formation. The deeper part of the defect, situated more cervically, is less affected by the condition than the outer occlusal part, and cusp enamel appears to be only mildly affected; cervical enamel always appears to be normal.

The diagnosis of MIH is usually made clinically and, to diagnose MIH, at least one of the first permanent molars has to be affected. The defects can also be seen in second primary molars, incisors and the tip of canines. If there are more affected molars and incisors, the defect could be considered to be more severe.

The prevalence of MIH

The earliest epidemiological study clearly identifying MIH was carried out on Swedish children in the late 1970s; it was published in 1987 (Koch et al., 1987). Although MIH as a term was not used until 2001, Koch et al described the affected permanent first molars as “cheese” molars with creamy-white to yellow-brown enamel opacities, or with disintegration in severe cases (Koch et al., 1987). The authors claimed then that the prevalence of the defects was increasing.
The decline in caries rates is perhaps one of the contributing factors to MIH becoming more readily seen and diagnosed (Crombie et al., 2009). MIH is one form of demarcated enamel defect (in addition to those caused by trauma to predecessors or caused by clear chronological causes), and, as such, it has been reported as part of older studies on enamel defects (Koch et al., 1987, Mackay and Thomson, 2005, Suckling and Pearce, 1984, Suckling et al., 1987, Suckling, 1989, Cutress et al., 1985). However, it cannot be determined with certainty that the enamel defects investigated in these studies were MIH. The introduction of the Developmental Defects of Enamel (DDE) index by the FDI (Federation Dentaire Internationale, 1982) and the inclusion of criteria for demarcated enamel defects helped in removing much of the confusion about different types of enamel defects.

Because the term MIH was only introduced in 2001 (Weerheijm et al., 2001b), this literature review focuses on studies published after 2000, with the exception of the study by Koch et al (Koch et al., 1987). In total, 28 studies are summarised in Table 2.3, with regards to where the study took place, the sample size, the age group, the examination method (when available in the published paper) and the prevalence of MIH reported. The Table is not meant to be a complete coverage of all the studies published on the prevalence of MIH, but rather more comprehensive coverage of the majority of the studies reporting its prevalence.

According to these studies, the prevalence of MIH ranges from 2.8% to 40.2%. The examination method does not seem to have an effect on the reported prevalence of MIH. Most of the studies have been conducted in European countries, where the prevalence of MIH ranges from 3.6% to 25.0% (Weerheijm and Mejare, 2003). There are also reports from Asia, Australasia, Africa and South America. However, to date, there are no reports from North America about the prevalence of MIH.
A systematic review by Jalevik in 2010 (Jälevik, 2010) stated that comparison of the findings from various studies were difficult because of the use of different indices and criteria, examination variability, methods of recording and different age groups. The wide range in prevalence reported in the different studies may reflect the real situation where different countries may have different prevalence. This possibility cannot be ruled out, especially because the aetiology of MIH has not yet been confirmed. In addition, the different assessment methods used in recording MIH, the differences between the examiners, the inclusion and exclusion criteria, and in the conditions under which the examinations were conducted, have most likely affected the reported prevalence from different studies.
Table 2.3. The reported prevalence of MIH in different countries.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample Size</th>
<th>Years age</th>
<th>Prevalence</th>
<th>Examination Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cho et al., 2008)</td>
<td>Hong Kong</td>
<td>2635</td>
<td>11-14 years</td>
<td>2.8%</td>
<td>In dental clinics</td>
</tr>
<tr>
<td>(Fteita et al., 2006)</td>
<td>Libya</td>
<td>378</td>
<td>7-8.9 years</td>
<td>2.9%</td>
<td>Using a lamp, in schools, teeth dried with gauze</td>
</tr>
<tr>
<td>(Kukleva et al., 2008)</td>
<td>Bulgaria</td>
<td>2960</td>
<td>7-14 years</td>
<td>3.6%</td>
<td>Using a lamp, wet teeth</td>
</tr>
<tr>
<td>(Dietrich et al., 2003)</td>
<td>Germany</td>
<td>2408</td>
<td>10-17 years</td>
<td>5.6%</td>
<td>Using a lamp, wet teeth</td>
</tr>
<tr>
<td>(Preusser et al., 2007)</td>
<td>Germany</td>
<td>1022</td>
<td>6-12 years</td>
<td>5.9%</td>
<td>Using a lamp, at school, wet teeth</td>
</tr>
<tr>
<td>(Parikh et al., 2012)</td>
<td>India</td>
<td>1366</td>
<td>8-12 years</td>
<td>9.2%</td>
<td>Wet teeth</td>
</tr>
<tr>
<td>(Weerheim et al., 2001a)</td>
<td>The Netherlands</td>
<td>497</td>
<td>11 years</td>
<td>10.0%</td>
<td>At schools</td>
</tr>
<tr>
<td>(Lygidakis et al., 2008)</td>
<td>Greece</td>
<td>3518</td>
<td>5-12 years</td>
<td>10.2%</td>
<td>Using dental light in a chair</td>
</tr>
<tr>
<td>(Muratbegovic et al., 2007)</td>
<td>Bosnia and Herzegovina</td>
<td>560</td>
<td>12 years</td>
<td>12.3%</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Calderara et al., 2005)</td>
<td>Italy</td>
<td>227</td>
<td>7-8 years</td>
<td>13.7%</td>
<td>At schools</td>
</tr>
<tr>
<td>(Kemoli, 2008)</td>
<td>Kenya</td>
<td>3591</td>
<td>6-8 years</td>
<td>13.7%</td>
<td>At schools</td>
</tr>
<tr>
<td>(Jasulaityte et al., 2008)</td>
<td>The Netherlands</td>
<td>442</td>
<td>9 years</td>
<td>14.3%</td>
<td>Using a dental light, dry teeth</td>
</tr>
<tr>
<td>(Päätäreanu et al., 2006)</td>
<td>Romania</td>
<td>681</td>
<td>8-11 years</td>
<td>14.5%</td>
<td>Wet teeth</td>
</tr>
<tr>
<td>(Jasulaityte et al., 2007)</td>
<td>Lithuania</td>
<td>1277</td>
<td>7-9 years</td>
<td>14.9%</td>
<td>At school, on school chair, using headlight and portable light, wet teeth, teeth brushed</td>
</tr>
<tr>
<td>(Mahoney and Morrison, 2009)</td>
<td>New Zealand</td>
<td>522</td>
<td>7-10 years</td>
<td>14.9%</td>
<td>In school classroom</td>
</tr>
<tr>
<td>(Kuscu et al., 2008)</td>
<td>Turkey</td>
<td>147</td>
<td>7-9 years</td>
<td>14.9%</td>
<td>Using a dental light, dry teeth</td>
</tr>
<tr>
<td>Reference</td>
<td>Location</td>
<td>Sample Size</td>
<td>Age Range</td>
<td>Proportion (%)</td>
<td>Description</td>
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<tr>
<td>(Balmer et al., 2011)</td>
<td>Northern England</td>
<td>3233</td>
<td>12 years</td>
<td>15.9%</td>
<td>At school, using a desk lamp, mirror</td>
</tr>
<tr>
<td>(Gómez et al., 2012)</td>
<td>Spain</td>
<td>505</td>
<td>6-14 years</td>
<td>17.9%</td>
<td>Prophylaxis, using dental light, wet teeth</td>
</tr>
<tr>
<td>(Jälevik et al., 2001a)</td>
<td>Sweden</td>
<td>516</td>
<td>7-8 years</td>
<td>18.4%</td>
<td>At school, using a lamp, wet teeth</td>
</tr>
<tr>
<td>(Mahoney and Morrison, 2011)</td>
<td>New Zealand</td>
<td>235</td>
<td>7-10 years</td>
<td>18.8%</td>
<td>In school classroom</td>
</tr>
<tr>
<td>(Leppaniemi et al., 2001)</td>
<td>Finland</td>
<td>488</td>
<td>7-13 years</td>
<td>19.3%</td>
<td>Using dental light in a dental chair, wet teeth</td>
</tr>
<tr>
<td>(da Costa-Silva et al., 2010)</td>
<td>Brazil</td>
<td>918</td>
<td>6-12 years</td>
<td>19.8%</td>
<td>At schools</td>
</tr>
<tr>
<td>(Savisit et al., 2008)</td>
<td>Thailand</td>
<td>479</td>
<td>6-7 years</td>
<td>20.3%</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Ghanim et al., 2011)</td>
<td>Iraq</td>
<td>823</td>
<td>7-9 years</td>
<td>21.5%</td>
<td>At school, teeth brushed and dried with cotton roll, using portable light and mirror</td>
</tr>
<tr>
<td>(Wogelius et al., 2008)</td>
<td>Denmark</td>
<td>745</td>
<td>6-8 years</td>
<td>37.3-48.4%</td>
<td>In dental clinics, wet</td>
</tr>
<tr>
<td>(Soviero et al., 2009)</td>
<td>Brazil</td>
<td>292</td>
<td>7-13 years</td>
<td>40.2%</td>
<td>Using a lamp, in schools, wet teeth</td>
</tr>
</tbody>
</table>
Possible aetiological factors in the occurrence of MIH

MIH refers to demarcated, qualitative defects of enamel of systemic origin, affecting one or more permanent molars (usually the first permanent molars) with or without involvement of the incisor teeth (Weerheijm et al., 2001b). In view of the lack of definite chronological distribution of enamel defects, it can be defined as hypomineralisation of systemic origin. Although MIH can affect multiple teeth, it neither is completely chronological in expression (such as with tetracycline staining or linear enamel hypoplasia) nor does it affect the entire dentition, such as in amelogenesis imperfecta (Aldred et al., 2003, Glimcher et al., 1977).

Although a wide variety of factors have been implicated in the aetiology of developmental enamel defects, the aetiology of MIH remains unclear. It has been associated with undetermined environmental and genetic factors that disrupt normal amelogenesis of the affected teeth. A number of possible aetiological factors have been suggested for MIH. Alaluusua (Alaluusua, 2010) recently conducted a systematic review and evaluated the strength of evidence for the possible aetiology of MIH. The paper concluded that there is currently insufficient evidence to support any of the proposed aetiologic factors, due to the weakness of the evidence.

Some of the possible aetiologies that have been suggested to be associated with this condition are high fever, oxygen deficiency at birth, prenatal and perinatal sickness, respiratory infections in the first three years of life, or nephritic diseases. MIH has also been suggested as being associated with toxins and antibiotic consumption, malnutrition, intestinal inflammation, diarrhoeas and hypoparathyroidism occurring during the same crucial period. Fearne et al (Fearne et al., 2004) suggested that the disturbances could be more chronic in nature over a longer period, based on the random distribution of hypomineralisation in the affected teeth. A family history of enamel defects is
commonly reported for MIH, but the association has not been shown to be statistically significant (Whatling and Fearne, 2008).

Farah et al (Farah et al., 2010b) found serum proteins, albumin and antitrypsin in MIH-affected enamel. It has been demonstrated in animal studies in rats by Robinson et al (Robinson et al., 1992, Robinson et al., 1994) serum albumin was discovered in enamel defects in rats similar to those in human MIH enamel. Serum albumin binds and inhibits enamel crystal growth, a key process in enamel formation (Robinson et al., 1992, Robinson et al., 1996). Farah et al (Farah et al., 2010b) demonstrated the presence of serine proteinase inhibitors, antitrypsin and antithrombin in MIH enamel. Serine proteinase is a critical enzyme in enamel formation that degrades enamel matrix proteins, allowing mineralisation to proceed. The combined effect of serum albumin and serine proteinase inhibitor antitrypsin may explain the greater organic content, lower mineral content and poor mechanical performance of MIH enamel.

Serum protein could be incorporated into enamel during its formation subsequent to trauma, or it could diffuse into enamel defects from saliva and crevicular fluid after eruption. The latter process can be excluded if the proteins present in MIH enamel are found in higher concentrations in blood than in saliva. If proteins present in MIH enamel are primarily from blood, they may have been incorporated during enamel formation (Farah, 2009), or after enamel formation is complete, either during tooth eruption or from gingival bleeding posteruptively. It is thought that blood is unlikely to enter enamel during eruption, because haemorrhage does not usually occur during eruption unless pericoronitis develops. It is also thought to be unlikely for blood from gingival bleeding to enter hypomineralised enamel (Farah, 2009). Although other reports have disputed this, Farah also suggested that serum proteins do not penetrate demineralised or hypomineralised enamel, and can only be incorporated during the dynamic process of demineralisation and remineralisation (Farah et al., 2010b). Assuming that blood components are only incorporated in enamel during formation (as a result of a traumatic insult),
they should be distributed according to the morphology of the MIH defects, following the incremental lines of Retzius. After enamel has already formed, the blood components are unlikely to follow this morphology, and penetration will be limited because exposure will be brief (Farah et al., 2010b).

It was hypothesised that MIH is of traumatic origin, most likely physical in nature that occurs around the time of birth, which resulted in serum and blood to leak into developing enamel and interfere with its mineralisation (Farah, 2011). However, they found it was not possible to accept or reject the hypothesis. The findings of their study suggested that serum or blood proteins leak into MIH enamel during the maturation stage of enamel development in the occlusal part of the first permanent molar (Farah, 2011).

Aetiological factors, as suggested by Alaluusua (2010), can be subdivided into the six categories (modified from (Alaluusua, 2010) of (1) pre-, peri- and post-natal events, (2) childhood illnesses, (3) antibiotics, (4) environmental toxicants, (5) breast-feeding, and (6) exposure to fluoride (Alaluusua, 2010).

**Pre-, peri- and post-natal events**

Malnutrition and health problems during pregnancy, birth and the neonatal period have been reported to contribute to a higher incidence of enamel defects in the primary dentition; however, the specific aetiological factor(s) have not been identified and may prove difficult to isolate due to the coexisting or closely related nature of these aetiological factors (Aine et al., 2000, Takaoka et al., 2011, Rugg-Gunn et al., 1998). Associations between pre-, peri- or neonatal problems and enamel defects in primary teeth have been demonstrated in several studies (Drummond et al., 1992, Lai et al., 1997, Aine et al., 2000, Rugg-Gunn et al., 1998, Seow, 1996). However, at this stage, the
role of these factors in the aetiology of defects in the permanent dentition remains unclear.

_Prenatal periods._ Reviews have reported that there is some evidence that medical problems during pregnancy are associated with MIH. In 2008, authors of two studies reported that medical problems were more common in mothers of MIH children than in mothers whose children did not have MIH (Whatling and Fearne, 2008, Lygidakis et al., 2008). In a survey of 109 children in the UK, Whatling and Fearne (Whatling and Fearne, 2008) found that MIH was significantly more common in children whose mothers had medical problems during pregnancy (37% in MIH group and to 17% in the control group). However, this study is likely to have been underpowered.

_Perinatal periods._ In the perinatal period, different medical conditions alone (or in combination) may affect a child. In a study by Lygidakis (2008) in Greek children, MIH was more frequently seen in the case group, where the most common perinatal problems/conditions were Caesarean section, prolonged delivery, premature birth or twinning were reported (Lygidakis et al., 2008). However, a study in UK children, and a German study found that perinatal problems could not be linked with MIH (Whatling and Fearne, 2008, Dietrich et al., 2003).

_Hypoxia._ Hypoxia is a pathological condition in which the body is deprived of adequate oxygen supply. Hypoxia can be associated with birth problems such as prematurity, respiratory distress and excessively prolonged duration of labour. Respiratory distress is a syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs. As the disease progresses, the baby may develop ventilatory failure (rising carbon dioxide concentration in the blood) leading to lack of oxygen supply to tissues. Several studies have suggested that a lack of oxygen in active ameloblasts could be the causative factor of MIH or opacities

In a study in rats, hypoxia was induced by maintaining the rats in a hypobaric chamber at 0.5 atm for 24 hours (Baumgardner et al., 1996). Oxygen tension markers showed little variation in mature ameloblasts of the test rat incisors than in the control rats while hypoxic disturbances were observed in the cells of the pulp and surrounding periodontium. This study suggested that short periods of hypoxia (respiratory acidosis) does not cause enamel defects. However, in another study in rats (Whitford and Angmar-Månsson, 1995), a long period of oxygen shortage showed that hypoxia induced by 10 percent carbon dioxide (CO₂) for 42 days caused enamel hypomineralisation in rat incisors.

**Hypocalcaemia.** Hypocalcaemia may occur not only in the perinatal period but also in the prenatal and postnatal periods. Jalevik et al (Jälevik et al., 2001c) demonstrated that the calcium concentration was lower in MIH lesions, which suggests that they may be caused by impaired calcium metabolism in the ameloblasts. Hypocalcaemia can be associated with maternal diabetes, vitamin D deficiency during the prenatal and/or perinatal period and prematurity. A prospective study by Aine et al (2000) demonstrated that MIH-like lesions and enamel hypoplasia were significantly more common in premature infants than in controls (Aine et al., 2000).

**Postnatal period.** Several studies have suggested that postnatal medical problems are associated with MIH. In a cohort study by Jalevik et al (2001) in 8-year-old Swedish children, an association between diseases at 0 to 1 year of age and subsequent MIH was only found in boys (Jälevik et al., 2001b). A study of Dutch children demonstrated that more of those with MIH had had illnesses during the first four years of life than those without MIH (Beentjes et al., 2002). Several studies have found no association between MIH and medical problems during pregnancy, mode of delivery, or complications during
delivery (Jälevik et al., 2001b, Muratbegovic et al., 2007). This was the case in a case-control study of MIH by Beentjes (2002), and Whatling and Fearne (2008) failed to demonstrate any relationship between MIH and delivery complications, delivery requiring induction, mode of delivery, birth weight or neonatal jaundice.

In a study in Australian children, Arrow (Arrow, 2009) demonstrated that children (84%) who had required medical care during the neonatal period were more affected by MIH-like defects than children (69%) who were healthy during infancy. This association applied to illnesses that occurred in the first 12 months of life, while subsequent illness had no significant effect on the occurrence of MIH. In a matched control study in Swedish children, Brogårdh-Roth et al (Brogårdh-Roth et al., 2011) demonstrated that MIH was more common in children born preterm (38%) than in children who were born at term (16%). However, other studies have failed to demonstrate any relationship between MIH and prematurity (Jälevik et al., 2001b, Beentjes et al., 2002, Muratbegovic et al., 2007).

**Exposure to environmental toxicants in the first two to three years of life**

The most commonly mentioned and discussed environmental contaminants have been polychlorinated biphenyls (PCBs) and dioxins (Alaluusua et al., 1996a, Jan and Vrbic, 2000, Jan et al., 2007). Accidental exposure to high levels of PCBs or dioxins in early childhood on children in eastern Slovakia was reported to be associated with demarcated opacity and/or hypoplasia (Jan et al., 2007). The source of these contaminants was said to be breast milk. These studies showed a dose-response relationship between the pollutant exposure (serum concentration) and the occurrence of developmental defects of enamel in permanent teeth. The prevalence of enamel defects was reported to be higher in children living in a PCB-contaminated area than in a comparison area in Slovenia (Jan and Vrbic, 2000). In a critical review of MIH
aetiology carried out by Crombie et al (2009), it was found that this is had the strongest aetiological evidence for MIH-like defects, although the evidence is still moderate at most.

In a study of Finnish children, Alaluusua et al (Alaluusua et al., 1996a) found that the frequency and severity of enamel defects associated with the total exposure to dioxins. It was also suggested that there was an association between long breast-feeding and enamel mineralisation defects in healthy children (Alaluusua et al., 1996b). Since these studies, three further ones, have found no association between breastfeeding and enamel defects (Jälevik et al., 2001b, Beentjes et al., 2002, Dietrich et al., 2003). In a Turkish study comparing the prevalence of MIH among children from areas polluted with dioxins and with that among children from areas clear of the pollution, there was no real difference (Kuscu et al., 2008). They concluded that MIH prevalence in their study was not associated with the level of dioxins in the environment. Following this report, Alaluusua and Lukinmaa (Alaluusua and Lukinmaa, 2006) re-evaluated their evidence and suggested that, at the current PCB and dioxin levels in the placenta and breast milk, there actually was no association with the occurrence of MIH.

In a recent report (Fagrell, 2011), in collaboration with the All Babies in Southeast Sweden (ABIS) prospective study, 17,000 children were examined, and the aetiological factors for severe demarcated enamel opacities in the first permanent molars were evaluated. The authors reported a positive association between severe demarcated opacities in the first permanent molars and breastfeeding for more than 6 months, late introduction of gruel and late introduction of infant formula. Moreover, a combination of these increased the risk of developing severe demarcated opacities five fold. The authors concluded that nutritional conditions during first 6 months of life may influence the risk of developing severe demarcated opacities in first permanent molars (Fagrell, 2011). These findings may also indicate that prolonged
exclusive breastfeeding may play a role, possibly because the infants may be no longer receiving enough nutrients from the breast milk alone.

**Medical conditions in the first three years of life**

This potential aetiology is the most studied one, and yet the findings are contradictory and the results are inconclusive. Jalevik et al (Jälevik et al., 2001b) reported that non-specific health problems such as upper or lower respiratory infections in early infancy may increase the risk of MIH. As discussed earlier, Lygidakis et al (Lygidakis et al., 2008) reported that 33.9% of children with MIH (from a group of 360 children) suffered from childhood illnesses in the first year of life, while it was only 12.5% in the matched control group. Childhood illnesses reported in the literature included otitis media (Beentjes et al., 2002), upper and lower respiratory tract infections (Beentjes et al., 2002, Jälevik et al., 2001b), asthma (Jälevik et al., 2001b), episodes of high fever, chicken pox (Whatling and Fearne, 2008) and urinary tract infections (Tapias-Ledesma et al., 2003).

Tapias-Ledesma et al (Tapias-Ledesma et al., 2003) reviewed the medical records of 48 children with enamel defects in their first permanent molars and 149 children without enamel defects. They reported that frequent medical care (especially for urinary tract infections) showed a strong association with enamel defects. However, although children with amelogenesis imperfecta were excluded from the study, the inclusion criteria did not specifically target MIH, instead following the DDE index criteria (Federation Dentaire Internationale, 1992), possibly therefore including other defects, such as hypoplasia and diffuse enamel defects, or definite chronological defects affecting more than the first permanent molars and incisors. Crombie et al (Crombie et al., 2009) concluded from their review that since the data were subdivided according to age, possibly making the sample number for each group very small, the statistical significance of the results was
questionable. Beentjes et al (2002) reported similar findings, but with MIH being associated with otitis media, pneumonia and high fever. In a study by Chawla et al (Chawla et al., 2008a), children with MIH showed histories of medical conditions that may be linked to MIH. However, no control group was used in that study, and direct comparison to healthy children could not be made.

Muratbegovic et al (Muratbegovic et al., 2007) compared matched groups of 69 twelve-year old children in Bosnia and Herzegovina with and without MIH. They did not demonstrate any significant associations between MIH and common childhood illnesses (including urinary tract infections, otitis media, high fever, asthma, bronchitis, pneumonia, tonsillitis or the use of antibiotics), whether separately or in combinations. In a similar study in German children, Dietrich et al (Dietrich et al., 2003) obtained similar findings. Similar study in a group of UK children by Whatling and Fearne included all the previously mentioned childhood illnesses as well as other illnesses, vaccinations and allergies, and found only that the occurrence of chicken pox between the age of 3 and 3.99 (P=0.047) showed a significant association with the occurrence of MIH (Whatling and Fearne, 2008).

A study by Dietrich et al (Dietrich et al., 2003) suggested the possible role of vitamin D deficiency and rickets in the aetiology of MIH, because mild vitamin D deficiency may cause enamel hypomineralisation without the classical signs of rickets. However, that study found no relationship between vitamin deficiency and MIH. Similar findings were reported in a matched case-control study in Bosnian children (Muratbegovic et al., 2007).

Although several studies have investigated the possible aetiology of MIH, the strength of the evidence is limited. This is because all of the studies so far have been retrospective studies, depending on parental recall of their children’s medical histories, or have depended on accessing records of unknown quality (Whatling and Fearne, 2008, Crombie et al., 2009).
The use of antibiotics in the first three years of life

The possible association of MIH with antibiotic use is still based on weak evidence. Only some studies have linked antibiotic use with MIH (Jälevik et al., 2001b, Beentjes et al., 2002, Whatling and Fearne, 2008, Laisi et al., 2009). Laisi et al (2009) suggested that the use of amoxycillin or erythromycin might be a causative factor in the occurrence of MIH. This is based on a survey and an animal study. In their survey of 141 children, only 23 children (16.3%) had MIH and it was found that MIH was more common among those who had taken amoxycillin or erythromycin during the first year of life. No association with other antibiotics was found. The possibility that other confounding factors (such as the infections or fevers) may be related was not assessed. In a UK study, it was found that MIH was more common among children who only received amoxycillin during the first four years of life, but not in children who received mixed antibiotics including amoxycillin (Whatling and Fearne, 2008).

In a study in mice, developing teeth isolated were allowed to grow in a culture medium. The media were divided into a control group without the use of amoxycillin and study groups with varying concentrations of amoxycillin (Laisi et al., 2009). The study groups showed more enamel growth than the control group. They suggested that this ‘excessive’ growth may mean that amoxycillin caused accelerated enamel growth, not allowing for adequate mineralisation. However, the authors did not demonstrate excessive thickening of enamel and suggested that this was possibly due to bacterial contamination preventing normal enamel growth in the control group. Even if the study did demonstrate amoxycillin’s detrimental effect on mice enamel formation, it does not necessarily mean that amoxycillin is a cause of MIH in humans. The authors noted that, in a classic study where MIH was first reported in Sweden in the early 1970s (Koch et al., 1987), if antibiotics had been involved, it could not have been amoxycillin, because it was not available in Sweden before 1975.
Whatling and Fearne (2008) found there were no differences between children with or without MIH, whether or not they had taken antibiotics and the number of antibiotic courses (Whatling and Fearne, 2008). Looking at individual antibiotics, only amoxycillin was shown to have been taken more in children with MIH. There was no association with other types of antibiotics. Similar results were reported by Jalevik et al (Jälevik et al., 2001b). Tapias-Ledesma et al (Tapias-Ledesma et al., 2003) and Muratbegovic et al (Muratbegovic et al., 2007) showed no association between any type of antibiotics and MIH. None of the studies have determined whether childhood infections (and associated fever) or the treatment with an antibiotic might be a causative factor. Therefore, the probability of any association with amoxycillin is likely to have been because of its very common use for childhood infections, and so it may be the infections (and associated fever) themselves as demonstrated in a study by Suckling (Suckling et al., 1987, Suckling and Pearce, 1984).

The aetiology of MIH remains unclear and it is impossible at this time to label any one factor as being an aetiological one because of non-specific, weak and conflicting reports about the aetiology of MIH. Generally, almost all the studies that have explored the possible aetiological factors behind MIH have agreed that there is no strong and valid support for any aetiological factor(s) (Arrow, 2008, Crombie et al., 2009, Whatling and Fearne, 2008, Jälevik et al., 2001b, Mathu-Muju and Wright, 2006, Muratbegovic et al., 2007, Preusser et al., 2007, Willmott et al., 2008). MIH may have a multifactorial aetiology, with factors acting together or even synergistically (Crombie et al., 2009, Alaluusua, 2010, Fagrell, 2011). There may be different types of MIH, and there may be a genetic predisposition associated with one or more of a range of systemic insults occurring at a susceptible stage in the development of specific teeth.
Severity classification of MIH

MIH is defined as a hypomineralisation of systemic origin of one to four permanent first molars frequently associated with affected incisors (Weerheijm et al., 2001b), and the severity of MIH varies among patients and also within a patient. Enamel opacities are considered as the mildest form of MIH and premature extractions and atypical restorations as the most severe manifestation of MIH (Weerheijm et al., 2001b). Different classification schemes for MIH severity have been used in different studies. Usually, there is no evidence that the classification scheme used is valid and reliable. Mejare et al (Mejare et al., 2005) classified the severity of MIH defects mainly according to the colour of the enamel, with sound enamel having a score of 0, white/opaque enamel 1, yellow or brown enamel 3, and post-eruptive breakdown regardless of the colour of the enamel 4. The teeth were not examined directly by the researchers; they used clinical photographs taken at the time of the patient’s first visit. Two studies (Jasulaityte et al., 2007, Lygidakis et al., 2008) used a similar simplified classification with only two categories: “mild” when enamel showed discoloration, and “moderate/severe” when post-eruptive breakdown or atypical restorations were present. Chawla et al (2008) used a similar two-category classification, where the teeth were categorized as “mild” when the colour was white-opaque, and “moderate-severe” when the teeth were yellow/brown and/or with post-eruptive breakdown.

In a German study (Preusser et al., 2007), the classification system was confusing and the categories not clear. The authors classified the tooth into “Degree 1” if it showed opaque, yellow or brown enamel in the ‘chewing surface and upper part of the crown’. “Degree 2” covered teeth with yellow/brown enamel ‘affecting more or less all the cusps on the top of the crown, but with only slight loss of substance’. “Degree 3” covered teeth with extensive post-eruptive enamel breakdown. This category covered ‘large-scale
mineral deficiency’ with yellow/brown discoloration and ‘defects in crown morphology resulting from extensive loss of enamel’.

Fteita et al (Fteita et al., 2006) and Leppäniemi et al (Leppäniemi et al., 2001) took previous treatment history into account and classified teeth with change in lucency or colour in the “mild defects” category, and post-eruptive breakdown of enamel in the “moderate” category. The “severe defects” category included post-eruptive breakdown complicated by dentinal caries, the presence of atypical restorations and the presence of extracted first permanent molars. Other studies took treatment needs into account also. Jälevik et al (Jälevik et al., 2001b) classified MIH teeth into “mild” defects when the surface was hard; “moderate” when there was a change in colour and minimal breakdown of enamel not requiring restorations; and “serious” when there was more extensive post-eruptive breakdown and need for restoration. This classification was adopted in another study (Dietrich et al., 2003).

In 2008, a complete paper dedicated to the description of a new severity index was published (Chawla et al., 2008b), introducing the first ordinal index for MIH. The first permanent molars are scored on four parameters (Table 2.4). The scores are then added up for all the first permanent molars and the total score is divided by the number of the erupted first permanent molars to give the final numerical reading for the particular person.
| Presence of first permanent molar | Unerupted = 0  
Erupted = 1 |
|----------------------------------|----------------|
| Extent of hypomineralisation      | None = 0  
Mild (white-opaque) = 1  
Moderate-severe (yellow/brown teeth and/or teeth with post-eruptive breakdown) = 2 |
| Sensitivity                      | None = 0  
Sensitive = 1 |
| Number of restorative procedures  | None = 0  
One = 1  
Two = 2  
Three or more = 3 |

**Table 2.4** MIH severity index (Chawla et al., 2008b)

The authors labelled their index as a ‘preliminary’ index only; this is because, just like any other index, it requires more research and testing before its validity and reliability can be confirmed.

**Clinical implications of MIH- problems and management**

**Problems and management**

MIH presents a set of problem sometimes requiring a multi-disciplinary approach to the management. It has been associated with a number of problems for treatment for the patients themselves. Dental sensitivity and pain, post-eruptive enamel breakdown, poor aesthetics in affected incisors, difficulty in achieving proper local anaesthesia, dental fear and anxiety associated with pain, difficulties in restoring the teeth and dental caries (Weerheijm, 2003) are among common problems presented by MIH. Because MIH becomes apparent only with the eruption of the permanent first molars and permanent incisors, significant dental treatment may be required at the ages of six to eight years. In such a young age group, this can be a challenge and may lead to dental anxiety (Jälevik and Klingberg, 2002, Weerheijm, 2004). In a survey of the members
of the European Academy of Paediatric Dentistry (EAPD), the majority of respondents considered MIH to be a problem for the dentist (Weerheijm and Mejare, 2003).

Because the enamel of teeth affected with MIH is less dense and may be porous and discoloured, some MIH-affected teeth have greater sensitivity to temperature changes or mechanical stimuli, and are subject to post-eruptive breakdown (Jälevik and Klingberg, 2002, Weerheijm, 2004, Willmott et al., 2008). Due to this greater sensitivity, a simple procedure such as brushing the teeth or drinking a cold or hot beverage may be difficult for children with MIH, even when the enamel is not broken down. The reasons for greater sensitivity are not clear. Weerheijm et al (Weerheijm, 2003) suggested that the aetiology of sensitivity is physiological, based on the repeated small pain stimuli. Rodd et al (Rodd et al., 2007) demonstrated quantitative changes in the pulp, indicative of an inflammatory reaction underneath MIH enamel. A mild inflammation in the pulp results in heightened excitability and sensitivity (Närhi et al., 1994, Orchardson and Peacock, 1994), and may prevent local anaesthesia being achieved easily (Fayle, 2003). Hypomineralised teeth have been shown to be difficult to anaesthetise, and this can result in discomfort to the child during dental treatment (Jälevik and Klingberg, 2002). It has been recommended to supplement local anaesthesia with sedation or relative analgesia when local anaesthesia on its own does not work (Mathu-Muju and Wright, 2006, Shargill and Hutton, 2007, William et al., 2006b). It may also be useful to use systemic pain control for restorative care in these patients.

The greater enamel porosity in MIH enamel (as shown by polarised light microscopy (Jälevik and Norén, 2000), and enamel breakdown exposing the sensitive dentine, as well as wide dentinal tubules at a young age) are suggested to be another reason for the greater sensitivity (Rodd et al., 2007). Post-eruptive breakdown usually occurs shortly after eruption, subsequent to occlusal loading (Weerheijm, 2003). This loss of tooth substance due to post-eruptive breakdown often causes severe discomfort during eating and tooth
brushing, which increases the risk of plaque accumulation and dental caries (Weerheijm, 2004) and further compromises the affected teeth.

No direct association has been observed between dental caries and MIH, but, as mentioned earlier, the greater sensitivity of MIH molars may result in the child avoiding brushing (Weerheijm, 2003). The irregular tooth structure following post-eruptive breakdown may also result in greater plaque retention and a higher risk of dental caries (Weerheijm, 2004). MIH teeth can be very sensitive and require early management, since rapid breakdown of tooth structure may occur, giving rise to acute symptoms and the need for more complicated treatment. Treatment needs will usually depend on the extent of the defects, the degree of tooth eruption, the symptoms and the ability of the patient to cope with care, and the oral hygiene and diet habits of the patient, because the affected teeth are at a higher caries risk and post-eruptive breakdown due to its porosity. Management ranges from using topical fluorides to encourage further mineralisation to the use of adhesive materials to seal the enamel and restore defects, or extraction of the severely affected teeth. Extraction of the teeth may be planned as part of orthodontic treatment (Lygidakis, 2010, Lygidakis et al., 2010).

Children with MIH may also complain about the appearance and colour of the affected incisor(s) (Fayle, 2003). Therefore, aesthetics should also be taken into account during treatment planning. Apart from the restorative difficulties faced by dental clinicians, children with MIH have been reported to have higher levels of dental fear and anxiety, and these behaviour-related problems may be related to pain experienced by the children during multiple treatment appointments, because many experience inadequate anaesthesia or even have treatment without local anaesthesia. Children with MIH have been shown to receive more dental treatment than unaffected children (Jälevik and Klingberg, 2002, Kotsanos et al., 2005). Jalevik et al (2002) found that 97% of children with teeth affected by MIH had experienced restorative treatment in their first permanent molars, with the majority having treatment multiple times
due to loss of fillings, marginal breakdown, or recurrent caries. Twenty eight percent had had extractions of one or more first permanent molars. On average, children with teeth affected by MIH, underwent treatment for their first permanent molars nine to ten times more than children with no affected teeth. Forty four percent of children with MIH had demonstrated behaviour management problems, most likely related to the high number of treatment episodes, and the painful experiences during treatment with inadequate local anaesthesia (Willmott et al., 2008). A similar study conducted in Australia (Chawla et al., 2008a) found that children with unaffected molars received only preventive treatment while 40% of those with MIH-affected molars underwent restorative treatment. Multiple restorations were required in 6% of the affected molars, and 8% required extractions. In summary, MIH molars require more visits, there is higher expense and more invasive treatment, and there is a demonstrated higher failure rate in the restorations.

It is therefore very important to diagnose MIH as early as possible in order to reduce the vulnerability of the MIH-affected molars to breakdown or other symptoms by focusing on early prevention and management. Early management should include explanation of the condition and its associated problems to the child and the parents. Reassurance should be given, because the other teeth are not affected by MIH (Weerheijm, 2003). Treatment planning for these children should also consider the long-term prognosis of the MIH-affected teeth and will, in some cases, involve a multi-disciplinary approach. The key to successful management of MIH is good treatment planning, encouragement of the child, and parental cooperation with the management that is needed.
**Dentino-pulpal complex considerations and the management of MIH-associated sensitivity**

Children with MIH-affected teeth suffer from dentine hypersensitivity from normally innocuous thermal, mechanical and osmo-chemical stimuli due to the presence of porous enamel and sometimes, exposed dentine (Jälevik and Klingberg, 2002). In 2007, Rodd et al reported that changes in pulpal innervation, vascularity and immune cell accumulation were indicative of an inflammatory response (Rodd et al., 2007). These are based on the immunocytochemical findings in extracted hypomineralised permanent first molars with recorded sensitivity to hot, cold, sweet or mechanical stimuli. In addition, the porous enamel may favour ingress of bacteria and bacterial contaminants (Fagrell et al., 2008), resulting in chronic inflammation of the pulp (Rodd et al., 2007). Following tissue inflammation, a variety of morphological and cytochemical neuronal changes may occur; these include neuronal branching and altered expression of neuropeptides and ion channels that seem to result in an overexpressed dental sensitivity (Rodd et al., 2007).

From a clinical point of view, these findings support early intervention in order to avoid development of pulpal inflammation and associated hypersensitivity. Toothpaste and/or chewing gums with mineralising materials (such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) (Baroni and Marchionni, 2011 ) or the application of desensitizers (2% potassium nitrate plus 2% sodium fluoride) or sealers) may be indicated (Lygidakis, 2010, Lygidakis et al., 2010). It is recommended that the child uses at least 1000 ppm or 1450 ppm fluoride toothpaste instead of low-fluoride children’s toothpaste (Willmott et al., 2008). Some papers now advocate the use of CPP-ACP to help mineralise the surface/subsurface layer, thus reducing the sensitivity associated with the porous enamel (Willmott et al., 2008, William et al., 2006b). Similarly, topical fluoride application with neutral fluoride products may help mineralise the enamel and reduce its sensitivity (William et al., 2006b, Mathu-Muju and Wright, 2006, Willmott et al., 2008).
However, none of these products has been investigated for use in children with MIH, so their efficacy is not known at this time.

Dental pain and the severity of hypomineralisation or enamel loss in MIH-affected teeth are the major determinants of the choice of treatment (William et al., 2006b). The most conservative interventional treatment consists of bonding a tooth-coloured material to the tooth to protect the affected tooth from further wear, breakdown or sensitivity, although the nature of the enamel may prevent formation of an acceptable bond if the bonding is not extended to contiguous areas of healthy enamel (William et al., 2006a). Less conservative treatment includes stainless steel crowns, permanent cast metal onlays, or extraction as part of orthodontic treatment.

**Clinical management of MIH**

It is recommended that the management of MIH focus on the three aspects of controlling the sensitivity, short-term management, and definitive management. In 2006, William et al (William et al., 2006b) proposed a six-step management approach for MIH. The approach consisted of first identifying children at risk for MIH, followed by early diagnosis, mineralisation and sensitivity control, prevention of caries and post-eruptive breakdown, restoration or extraction, and, finally, long-term maintenance. According to William et al (William et al., 2006b), identification of children at risk for MIH should be made prior to first permanent molar eruption, based on medical history and radiographs. However, this is very difficult at the present time when the aetiology is not well understood. Muratbegovic et al (Muratbegovic et al., 2007) suggested that it was not possible to make a valid prediction of whether or not a child would develop MIH based on his or her medical history. Because MIH also presents with a range of severities and mineral densities and radio-densities (Fearne et al., 2004), it would not be possible to diagnose more
The second primary molars and first permanent molars have a shared period of development and mineralisation, and a relationship between hypomineralised second primary molars and MIH has been observed in some (Weerheijm, 2003). This is hypothesised to be because development of the second primary molar and the first permanent molar starts at similar times, but the maturation phase of the permanent molar is considerably longer (Butler, 1967). If any disturbance or risk factor occurs during this overlapping period, hypomineralisation might occur in both the primary and permanent dentitions (Aine et al., 2000).

In a Dutch study of 7893 children aged 5 to 6 years (Elfrink et al., 2012), an association between the occurrence of second deciduous molar hypomineralisation (9.0%) and MIH (8.7%) suggested a shared aetiology. The relationship between deciduous molar hypomineralisation (DMH) and MIH found in their study is an additional tool in the study of possible aetiological factors such as exposure to dioxins from breastfeeding, antibiotic use, perinatal problems, infectious diseases, and others (Alaluusua et al., 1996b, Alaluusua et al., 1999, Weerheijm et al., 2001b, Whatling and Fearne, 2008, Laisi et al., 2009) because they might lead to both DMH and MIH. Therefore, in clinical practice, it may be suggested that deciduous molar hypomineralisation (DMH) might clinically be used as a predictor for MIH because the second deciduous molars erupt 4 years earlier in life than first permanent molars. Children with DMH should be monitored for MIH, especially during the eruption of the first permanent molars and incisors.

In a systematic review by Lygidakis (Lygidakis, 2010) of the clinical management and treatment modalities in children affected by MIH, it was suggested that MIH should be approached by diagnosing the type of MIH-affected teeth (first permanent molars or incisors), and the severity of the
defects, then, the management of the first permanent molars without post-eruptive breakdown (PEB) or with post-eruptive breakdown; and/or incisors with different level of opacities should also be considered. The clinical guidelines for managing of children affected by MIH are summarised in Figure 2.2.
**Figure 2.2.** Flow chart illustrating clinical management approach of MIH children with a history of putative aetiological factors in the first 3 years (modified from Fagrell, 2011, Alaluusua, 2010, Crombie et al., 2009, Lygidakis, 2010)
The goals of restoring defective molar enamel are: (1) to restore the occlusion; (2) to decrease the sensitivity; (3) to prevent further enamel breakdown; (4) to decrease the risk of caries establishment; (5) to achieve correct interproximal contacts; and (6) supporting the remaining tooth structure. These are achieved mostly with extracoronal restorations. Several different restorative materials and techniques have been suggested in the literature for the management of MIH-affected molars.

In most MIH-affected molars, the shape and position of the restorations are somewhat different from restorations placed to treat dental caries, regardless of the material or restoration placed. This is because MIH defects often involve the outer slopes of the cusps, an unusual location for carious lesions. The presence of ‘atypical restorations’ in first permanent molars constitutes one of the criteria used in diagnosing MIH (Weerheijm et al., 2003). Unfortunately, neither the conventional cavity preparation recommendations nor the currently available restorative materials are entirely successful for restoring MIH defects (Mahoney, 2001) due to the high protein content of MIH enamel that interferes with bonding (William et al., 2006a).

Several reports have suggested using sodium hypochlorite (NaOCl) to denature the proteins in the surface layer of MIH enamel in an attempt to increase the bonding strength (Mahoney, 2001, Fayle, 2003, Mathu-Muju and Wright, 2006, William et al., 2006b). However, the evidence supporting the use of NaOCl is still weak, and some studies have shown that this can lead to cohesive failures because the bonded restorations pull the enamel apart. More studies are required before recommending the use of this procedure routinely.

Glass ionomer cement (GIC) has been recommended as an intermediate restorative material for defective MIH enamel due to the enamel’s poor etching profile (Jälevik et al., 2005). GIC was recommended for moderate
defects because it chemically bonds to enamel and therefore the restoration margins can be placed in affected but still hard enamel (Mahoney, 2001, Fayle, 2003, William et al., 2006b, William et al., 2006a). However, GIC restorations in MIH molars have shown significantly higher failure rates than amalgam and composite resin restorations (Mejare et al., 2005). Due to its compromised performance after extended use, placement of GIC as a restorative material may be recommended only in two cases: (1) an uncooperative patient for whom composite resin restoration is difficult; or (2) as interim restorations when teeth are planned for timed extraction or when more definitive treatment is planned later, such as under general anaesthesia (Mahoney, 2001, Fayle, 2003). Resin-modified GIC may be a better option for interim restorations than regular GIC, because it is easier to handle and offers more wear resistance (William et al., 2006b).

When placing any restoration (especially the more sensitive composite resin restorations) good isolation using rubber dam is very important (Mahoney, 2001). This is because a composite restoration placed without the use of rubber dam may be contaminated by saliva or blood, causing it to be compromised and its survival reduced even more than usual. Rubber dam may also help to isolate other MIH molars, decreasing their sensitivity from air and water during tooth preparation. For many of the molars, rubber dam cannot be placed because the tooth is badly destroyed or has only partially erupted. Therefore, interim restorations can be placed if the tooth is restored, but the child and family should be informed about the lower success rate that is likely.

Restoration of MIH defects has a relatively high failure rate (Jälevik and Klingberg, 2002, Chawla et al., 2008b). A retrospective study of treatment records of 36 MIH patients and 36 matched control patients by Kotsanos et al (Kotsanos et al., 2005) found that the mean DMFS was significantly higher in the MIH group. The MIH group children had three times more replacement fillings than the control group children. In addition, children from the MIH group showed 11 times more restorative treatment than the control group, more
invasive treatments (e.g. more stainless steel crowns), and more surfaces treated in individual molars. In the control group, no re-treatments were required for restorations; however, 17% of the fissure sealants required re-treatment. In the MIH group, 61% of amalgam restorations were replaced, 25% of the composite restorations required re-treatment, and none of the stainless steel crowns failed. It was suggested that composite was a better material to restore the atypical outline of the defective MIH enamel (William et al., 2006b, Fayle, 2003, Willmott et al., 2008). However, the use of composite restoration for cuspal replacement does have some problems, such as the polymerisation shrinkage and cuspal deflection. Composite use appears to be more successful where defective enamel is well demarcated, and confined to one or two surfaces and no cuspal replacement is indicated (Fayle, 2003). Composite resin restorations have shown a high success rate over an extended period of time when they is used within these recommendations (Lygidakis et al., 2003).

In a study comparing the microshear bond strength of composite resin to MIH enamel and sound enamel (William et al., 2006a), it was found that there is significantly lower bond strength to MIH enamel than with sound enamel. Acid etching produced deeper etch patterns in sound enamel than in MIH enamel, resulting in less micromechanical bonding to composite resin in the latter. The failure of bonding to MIH enamel was predominantly cohesive in nature; that is, the defective enamel fractured beneath the composite, rather than the composite being detached or adhesive failure occurring. The findings of this study should be considered with some caution, because microshear bond strength is basically a failure initiation test. It predominantly focuses the forces to the weakest point of a system and does not reflect the gradual degradation of the system in the oral cavity. Furthermore, there is a wide range of lowered mechanical properties in MIH enamel (Mahoney et al., 2004), and generalisations need to be made with caution. Mahoney et al (Mahoney et al., 2004) demonstrated that the mechanical properties of MIH-affected enamel were poorer than those of normal enamel. Some authors recommend complete removal of the defective enamel before placement of restorations (William et
al., 2006b, Willmott et al., 2008), because defective enamel breaks down under direct occlusal load, and it may also break down under indirect occlusal load transmitted through a restoration.

Intracoronal composite resin restoration may be used when there are small defects. It is preferable that all the defective enamel is removed and the cavity walls are placed in sound enamel (Shargill and Hutton, 2007). In mild-to-moderate cases, composite resin restorations have demonstrated good success rates (Lygidakis et al., 2003).

In moderately-sized defects, extracoronal restorations may be a better option, with a higher success and survival rate. Extracoronal restorations include stainless steel crowns and cast metal onlay restorations, with both demonstrating high success rates (Zagdwon et al., 2003). Preparation techniques for cast onlays are more exacting than those for stainless steel crowns but can be more destructive if all surfaces are prepared. More recently, it has been recommended to place stainless steel crowns with the most minimal preparation possible. Several studies have described the use of stainless steel crowns on permanent molars (Croll and Castaldi, 1978, Croll, 1999, Randall, 2002, Seale, 2002). Orthodontic separating rings can be placed interproximally a few days (and up to a week) prior to preparing the tooth in order to help open the contacts. This allows for less tooth preparation (Fayle, 2003). Onlays are more definitive restorations but have the disadvantage of initially being more expensive, and they require more than one visit (Zagdwon et al., 2003). However, their potential success and low need for restoration replacement probably makes them more cost-effective in the long term. They are also the least destructive of all extracoronal options.
Management of MIH-affected incisors

As suggested by Lygidakis et al (2010), when aesthetics are the main concern for an affected child, management of incisors affected by MIH can often be achieved with microabrasion (with or without bleaching) and the use of composite resin restorations or veneers. In the late mixed dentition, bleaching with carbamide peroxide alone may also be used for the affected incisors (Fayle, 2003). However, bleaching in younger children may induce hypersensitivity, mucosal irritation and enamel surface alteration (Joiner, 2006), so care must be taken with microabrasion because there will always be some loss of enamel (Sundfeld et al., 2007). In late adolescence, when the gingival margin has reached its adult position, porcelain veneers may be used to restore the aesthetic appearance of the affected incisor(s) if they are still an aesthetic problem (William et al., 2006b).

Extractions of MIH-affected molars with growth monitoring or as part of planned orthodontic treatment

The choice between restorative treatment and extraction depends on many factors, such as the age of the patient on presentation, the number and severity of the defects, potential growth and development consequences, the wishes of the child and parents and the ability of the child to manage treatment (Mejare et al., 2005). Some studies have suggested extracting moderately to severely affected first permanent molars (Mejare et al., 2005, Shargill and Hutton, 2007).

In a study of 76 patients with MIH, treated by 18 dentists in Sweden, the outcomes of treatment at 18 years of age were examined (Mejare et al., 2005). They reported that the extraction of molars with severe enamel defects gave good or acceptable occlusion results in a majority of the patients while conservative restorative treatment resulted in a need for additional treatment in
approximately half (48%) of the patients. The study also showed that the extraction of MIH molars did not have an effect on the sagittal relationship or midlines. They did note that 34% of the former patients (for whom one or more first permanent molars were extracted) underwent orthodontic treatment. It was not clear whether the extractions were the main reason behind the orthodontic treatment or whether there were other indications. Acceptable space closure after extraction was found to be similar in patients who received orthodontic treatment and those who did not. Irrespective of the type of treatment received, about 80% of the patients were satisfied with the outcome of their treatment. Since extractions have good results, good patient satisfaction, and did not have the problems of frequently failed restorations, Mejare et al (Mejare et al., 2005) recommended (based on the findings of this study) extracting molars with severe MIH defects. However, what was not clear from the small numbers in the study was what is the ideal timing for extractions and what level of monitoring is required in the long term. It was also not clear what defects were more likely to have longer-term problems with restorations.

In another study (Jälevik and Möller, 2007), it was shown that second permanent molars achieved a favourable position in the arch, with good contacts with the second premolars and good occlusion with the opposing teeth in almost all of the cases where first permanent molars were extracted at 8.5 to 9.5 years-of-age. Extraction at earlier or later ages showed favourable developmental outcomes in most cases as well, although some complications occurred (Jälevik and Möller, 2007).

From an orthodontic treatment point of view, first permanent molars are not the teeth of choice for extraction. Their posterior location in the arch and their size result in treatment taking longer to close spaces and retracting the anterior teeth takes longer. Moreover, first permanent molars are often key teeth for anchorage. In addition, the evidence for the preferred time of extraction is relatively weak (Williams and Gowans, 2003).
Around 8.5 to 9.5 years of age, the mesial drift potential for the second permanent molars is highest and the distal drift potential for the second premolar is minimal, making it the optimum age for the extraction of first permanent molars (Williams and Gowans, 2003). At around this age, the furcation of the roots of the lower second permanent molars is starting to form and calcify.

Shargill and Hutton (2007) and Williams and Gowans (2003) suggested some recommendations for the extraction of MIH-affected first permanent molars (Williams and Gowans, 2003, Shargill and Hutton, 2007). They recommended that consultation with an orthodontist before extraction of MIH-affected molar(s) is advisable. They suggested that affected lower first permanent molars be extracted when there is crowding in the dental arch, because more favourable contact is achieved between the erupting second permanent molar and the second premolar, relieving some of the crowding and allowing more space for the eruption of the lower third molar. If no crowding exists, the likelihood of an open contact is considerable, and the use of fixed orthodontic appliances may be needed. Generally, when extracting lower first permanent molars, it is often advisable to extract upper first permanent molars also (compensation extraction). This is because there is a potential for over-eruption of the upper first permanent molars preventing proper space closure by the lower second permanent molar. Otherwise, an upper fixed orthodontic appliance should be considered to control possible over-eruption. In cases of Class II malocclusion with anterior crowding, they recommended that there is usually no need for compensation extraction, because the upper first permanent molar eventually achieves proper occlusion with the lower second permanent molar.

In general, following the extraction of the upper first permanent molars only, upper second permanent molars achieve better and more predictable results than lower second permanent molars. There is usually no need for compensation extraction.
In cases of Class II malocclusion, ideally first permanent molars should be maintained until the eruption of the second permanent molars. Space created by the extraction can be utilised for retracting the teeth to reduce the increased overjet. No compensation extractions are required.

In Class III malocclusions, each case should be assessed individually. Generally, balancing and compensation extractions are not routinely recommended. In certain cases, when post-eruptive breakdown occurs before the optimum time for extraction is reached, or when the molars have not erupted fully, it may be advisable to temporarily restore the affected teeth until the proper time for extraction is reached. The condition of the entire dentition should be considered, especially the state of the second permanent molars and premolars.

A study by Mejare et al (2005) showed that some MIH-affected molars indicated for extraction required several visits before extraction because the affected molars were temporised until the optimum time of extraction was reached. This is because early extraction (before the calcification of the furcation of the second permanent molars roots) increases the risk of the second premolar drifting distally, especially when the premolar is distally inclined (Jälevik and Möller, 2007). Extraction of the second primary molar at the time of the extraction of the first permanent molar may help alleviate this problem (Williams and Gowans, 2003). On the other hand, if the extraction of the first permanent molars is done after the optimum age, it will usually result in the second permanent molars tipping mesially and rotating lingually.

In conclusion, extraction of severely affected MIH molar(s) should always be considered as part of long term treatment planning and management, because with proper planning, this management can have a very acceptable outcome.
Conclusion

Despite the number of studies published during recent years, the aetiology of MIH remains unclear. According to the available evidence from literature in relation to MIH, pre-, peri- and post-natal events increases the prevalence of developmental defects of enamel in general, particularly in the primary dentition. However, the relationship between MIH and these factors in the permanent dentition remains unclear and substantial amount of research is required to establish their role in the aetiology of MIH. Exposure to environmental toxicants (such as PCBs/dioxins) in the first two to three years of life does appear to be a risk factor for developing MIH-like defects but greater duration of breastfeeding itself does not appear to increase the prevalence of MIH. Medical conditions in the first three years of life and/or their treatment do appear to increase the prevalence of MIH, but again the evidence is weak and further research is required to clarify the specific cause(s) of their effects.

MIH is a recognised global dental problem with wide prevalence ranging from 2.8% in Hong Kong (Cho et al., 2008) to 40.2% in Brazil (Soviero et al., 2009), although there is little information from North America. With greater sensitivity, pain and associated dental fear and anxiety, MIH can results in problems with sensitivity and pain, aesthetics and a negative impact on the quality of life for the affected child. Apart from that, MIH also poses problems for dentists in achieving successful restorations or planning the timing of extractions. The lower mineral density and calcium content appears to compromise the mechanical properties of affected molars to withstand occlusal loads.

There remains a great deal of research to understand MIH-affected enamel. Therefore, as difficult and complex the resolution may be, all efforts should be made towards a better understanding of MIH, its aetiology, its structural features, and its mineral and organic contents, to allow for a more
accurate diagnosis and more appropriate methods to improve management including restorative techniques and materials.
Chapter III. Materials and Methods

Section 1. Background to the materials used

This section provides an overview of the theoretical background to the materials and methods used in the current study.

Ethical issues

The National Advisory Committee on Health and Disability Support Services Ethics (NEAC) functions as advice provider to the Ministry of Health on ethical issues of national significance regarding health and disability research and services, and to determine nationally consistent ethical standards and provide scrutiny for such research and services. Heath and Disability Ethics Committee are responsible for granting ethical approval of research projects involving human participants. Ethical approval for the current study was granted by the Lower South Regional Ethics Committee in March 2011 (Ref LRS/10/11/057) (Appendix 1) and the Southern District Health Board and Dunedin School of Medicine, Research Advisory Group (RAG) in April 2011 (Project ID 00690) (Appendix 2).

In New Zealand, recognition of Māori culture and the principles of the Treaty of Waitangi are also taken into account in all research. The University of Otago has a policy and process for research consultation with Māori that operates under the umbrella of the Treaty of Waitangi and the memorandum of understanding between Ngāi Tahu and the University of Otago. Approval from the Ngāi Tahu Research Consultation Committee was obtained in June 2010 (Appendix 3).
Study design

The current study is an individually matched case-control study, using a quantitative and descriptive approach. Two groups of participants were recruited: a case group consisting of children diagnosed with MIH recruited from the Paediatric Dentistry clinics in the School of Dentistry, University of Otago (n=46); and a control group (n=55) of participants individually matched for age, gender and ethnicity status.

Study participants

Children aged 6 to 12 years-of-age, who had been diagnosed with MIH, were identified from clinical records of Paediatric Dentistry patients. They and their mothers were invited to participate as the case participants.

The case participants were asked to identify three children “who are like them” (same gender and age) to participate in the study. The volunteered children were invited to participate as the matched control participants. If the volunteered children declined to participate or did not meet the inclusion criteria, children were identified from Oral Health Community Dental Service record matched for similar age and gender. The identified children were then invited to participate in the study.

Information sheets explaining the study and inviting the children and their parents to take part were either handed out in the clinics or were mailed using contact information. The information sheets explained that participation was voluntary and no identifying information would be used. They also explained that no information would be collected and recorded unless they chose to participate; they noted that, if they did not wish to participate, it would have no impact on any current or future dental care at the School of Dentistry.
or within the Community Oral Health Service (COHS). If they did not respond within two weeks, they were contacted by phone. For those with MIH who agreed to participate, a convenient time was organised to attend an appointment at the School of Dentistry in Dunedin.

Inclusion and exclusion criteria

Case participants included in the study fulfilled the following criteria:

- They were diagnosed with MIH (according to European Academy of Paediatric Dentistry (EAPD) guideline (Weerheijm et al., 2003))
- Were aged between 6 and 12 years-of-age
- The permanent first molars had erupted
- Born in Dunedin
- Written informed consent from the parent/caregiver to take part
- Written informed consent from the child participant

Control participants included in the study fulfilled the following criteria:

- Age-gender-socio-economic-status (SES) matched children who were not diagnosed with MIH

Case or control participants were excluded if they had been:

- Diagnosed with generalised enamel defects of genetic origin (amelogenesis imperfecta) or with enamel hypoplasia suggesting a chronologically related event or trauma
• Diagnosed with significant medical problems affecting growth and development
• Not born in Dunedin
• No consent or assent from the participant and/or parent.

Data collection

The study consisted of a comprehensive clinical oral examination and clinical photographs of the case participants and a brief clinical examination of the controls to confirm they did not have a diagnosis of MIH. For all participants, a structured interview with the birth mother, and a review of both the child’s and mother’s medical records were carried out to record the pregnancy, birth and neonatal histories to record any significant events that may have affected the developing enamel.

Information was recorded on coded forms to maintain participant anonymity. The codes for each participant and their mother were held in a secure electronic document and in hard copy by the main researcher (RAH) and her supervisors Professor B K Drummond (BKD) and Professor W M Thomson (WMT) in the Department of Oral Sciences.

The following information was recorded:

i. Details of the mother's health status during pregnancy, her smoking habits and the child’s health during the first four years of life. This was recorded in a structured interview with each participant’s mother (Appendix 9);
ii. A detailed history of the status of the child’s and mother’s health status during the perinatal period was recorded from the medical
notes with the help of the study advisors: a paediatrician, midwife and obstetrician;

iii. For the case participants, the following were recorded:
   c. Intraoral photographs of the occlusal surfaces of the first permanent molars and labial surfaces of the incisors if erupted.

Socio-economic status (SES) was assessed based on the participants’ school decile scores sourced from the New Zealand Ministry of Education website. A school’s decile score is an indication of the SES of most of the students attending that school. The most recent scores were calculated after the 2008 NZ census and are based on the student’s address. The participants’ current and past fluoridation status was obtained based on all addresses they had lived in. Dunedin city water fluoridation maps were used to determine if the participant was or had ever lived in optimally fluoridated areas.

All MIH participants were having the condition managed in the Paediatric Dentistry clinics. If any other clinical problems were identified requiring further assessment, this was noted for care in the clinics, or the appropriate medical or dental practitioner was contacted with the agreement of the participant and/or parent/caregiver. If there was no preference, a referral was made to the School of Dentistry or Community Oral Health Service with a copy to the participant and parent/caregiver.
Diagnostic criteria for MIH

In 2003, unified judging criteria for the diagnosis of MIH were introduced by Weerheijm et al (Weerheijm et al., 2003). The criteria consisted of the presence of demarcated opacities evident in the change of translucency/colour of the enamel, post-eruptive enamel breakdown, atypical restorations, extracted molars due to MIH, and failure of eruption of a molar or incisor (Appendix 11).

Weerheijm et al (Weerheijm et al., 2003) suggested the examination for MIH should be performed on clean wet teeth. The presence or absence of demarcated opacities, post-eruptive enamel breakdown, atypical restorations, extracted molars due to MIH, and failure of eruption of a molar or an incisor should be recorded.

In the current study, the criteria introduced by Weerheijm et al (Weerheijm et al., 2003) were used to identify the case participants.

Assessment of developmental defects of enamel (DDE)

Diagnosis of enamel defects has always been regarded as difficult. Various indices have been proposed for measuring enamel defects, including fluorosis. These indices can be divided into two main groups: specific fluorosis indices and descriptive indices encompassing three types of defects: demarcated and diffuse opacities and hypoplasia. Fluorosis indices are designed to measure defects of enamel due only to excessive ingestion of fluoride during critical stages of tooth development, described as enamel mottling or fluorosis. The most widely used index for measuring these defects is Dean’s Index (Dean, 1934). In using Dean’s Index, the examiner must first decide whether the defects present are due to excessive fluoride intake based
on a number of distinguishing characteristics, including an opaque white colour and a generalized distribution within the dental arch.

The confusion and difficulty in differentiating between fluoride and non-fluoride defects, and the confusion in classifying mottling, fluorosis, and enamel defects, have led to the development of a second group of indices covering all types of enamel defects. The indices were based on the clinical appearances of the enamel defects (Murray and Shaw, 1979). The development of these descriptive indices caused further confusion in reporting studies of enamel defects.

In order to overcome this problem, a Working Group of the FDI Commission on Oral Health, Research and Epidemiology was established in 1977. The group recommend the use of a descriptive index, the Developmental Defects of Enamel (DDE) Index. Ideally, a DDE Index should be simple to use to make the data collected meaningful and amenable to analyses and interpretation (Clarkson and O'Mullane, 1989). The DDE Index allows for measurement of demarcated opacity, diffuse opacity, and hypoplastic defects and their severity. The type of enamel defect (opacity, hypoplasia, discolouration), number (single and multiple), demarcation (demarcated and diffuse), and location of the defects on the buccal and lingual surfaces of teeth can be recorded (FDI Commission on Oral Health Research and Epidemiology, 1982).

The DDE Index has been used in several previous studies (Suckling and Pearce, 1984, Cutress et al., 1985, de Liefde and Herbison, 1985), and the results from these studies have shown that the DDE Index provides information on a wide range of defects, their distribution and location. However, the large amount of data generated has caused difficulties in presenting the results in a meaningful way, and in interpreting the results and comparing studies (Clarkson, 1989). Clarkson and O’Mullane (Clarkson and O'Mullane, 1989) recommended, for general screening purposes, that only three basic types of
defects be recorded (i.e. demarcated and diffuse opacities and hypoplasia). Defects that do not fall in this category, are scored as other defects. In carrying out epidemiological studies requiring both analytical and descriptive approaches, the new format of the DDE Index is used with codes from 1-9, either on index teeth or on all teeth, depending on the study. They also recommend that the teeth are examined in wet condition, using artificial light, and the light source should not be so strong as to create glare, which can mask the defects.

In the current study, the modified DDE index was used in recording the developmental defects of enamel status (World Health Organization, 1997, FDI Commission on Oral Health Research and Epidemiology, 1992).

**Assessment of dental caries**

The ideal method for diagnosing dental caries should be simple, non-invasive, reliable, valid, sensitive, specific, and based on lesion size and activity (Pitts, 1997). Caries diagnosis is complicated and requires a thorough patient history, visual examination, and sometimes supplemental tests such as radiographs, quantitative laser or light fluorescence (QLF), electrical conductance measurements (ECM), digital imaging fibre-optic trans-illumination (DIFOTI) or infrared (IR) laser fluorescence (Ekstrand et al., 1997, Ferreira et al., 2008, Ismail, 1997). No single caries-detection method can be used in isolation (Ferreira et al., 2008).

In a population, dental caries experience is assessed as a cumulative score of the number of decayed, missing or filled surfaces/teeth-dmfs/dmft for the primary dentition and DMFS/DMFT for the permanent dentition. The World Health Organization (WHO) diagnostic guideline for the “basic oral health survey” uses tactile and visual features to detect caries. In the guideline caries is defined as an “unmistakable cavity, undermined enamel, or detectably
softened floor or wall” and “caries that precedes cavitation is excluded because it cannot be reliably diagnosed” (World Health Organization, 1997). By restricting epidemiological surveys to this level of detection, the caries prevalence will be under-estimated (Pitts, 1997). In 2002, the International Consensus Workshop on Caries Clinical Trials (ICW-CCT) concluded that caries detection needs to occur at the pre-cavitated level (Pitts and Stamm, 2004). Hence, the International Caries Detection and Assessment System (ICDAS) was developed to provide a standardised system to measure varying levels of the caries process (Ismail et al., 2007). The lack of reliability with the diagnosis of pre-cavitated lesions was the main concern (Ismail, 1997, World Health Organization, 1997). However, when the examiners were thoroughly trained and calibrated prior to the study, this was not an issue (Nyvad et al., 1999).

In the current study, the WHO caries index was used in recording caries and restorative status (World Health Organization, 1997).

Clinical photographs

Clinical photographs taken before, during and after treatment form an essential part of patients’ records. Taken correctly, clinical photographs can offer more useful information about oral conditions, dental anomalies or defects that may be present and help to determine treatment required with the other clinical records.

The ideal clinical (dental) photographs should be able to be reproduced, with minimal image distortion and high image quality (McLaren and Schoenbaum, 2011). In general, this can be achieved through the use of digital single-lens reflex (DSLR) cameras with following features: true macro lens with a focal length of approximately 100 mm available, dual-point and ring macro flashes, customized white balance, RAW capability, and an APS-C
(“crop”)-sized sensor (McLaren and Schoenbaum, 2011). And, for intraoral clinical images, McLaren et al (McLaren and Schoenbaum, 2011) suggested the aperture to be set at f-32 on a manual exposure mode to allow sufficient exposure and depth of field.

In the current study, the camera used was a Nikon D8 fitted with a Nikon macro lens (AF-S Micro Nikkor 105mm 1:2.8 G ED) and a ring flash (Sigma EM-140 DG), and was set at f-32 on manual exposure mode with the shutter speed set at 1/80.
Section 2. Data collection and analysis procedures

This section details the methodology used for data collection and analysis.

Case participants

Seventy-two children aged 6 to 12 years, who had been diagnosed with MIH, were identified from clinical records in the School of Dentistry and they and their mothers were invited to participate in the study. An information sheet explaining the study and invitation to take part was sent to each child and their mothers using current contact information from the Paediatric Dentistry clinics, School of Dentistry, University of Otago (Appendix 4).

If they agreed to participate, an appointment was scheduled at the School of Dentistry, University of Otago. If they did not respond to the initial information sheet, they were contacted by phone and a convenient appointment time was scheduled if they wished to participate. A second information sheet was sent and followed up with a phone call to those who did not respond or could not be contacted previously. Recruitment of participants ceased once no additional case participants could be recruited.

Control participants

Children who agreed to participate in the study were asked to identify three children “who are like them” (same gender and age). All volunteered children who were not diagnosed with MIH were invited to participate as the matched control participants. Information sheet detailing the study and their reason for participation were sent (Appendix 5). Appointments were made for the volunteered children at the School of Dentistry, University of Otago. If the children and/or their mother declined to participate as the control participants,
children of similar ages, gender and from similar socioeconomic backgrounds who had not been diagnosed with MIH were matched using Community Oral Health Service records from children treated in the School of Dentistry Bachelor of Oral Health clinics. The children from primary schools in Dunedin who fulfilled the criteria and were scheduled to have their annual dental examinations in May and June 2012 were invited to participate as the control participants. These participants were assessed at School of Dentistry to check they did not have MIH and interviews with their mothers were done either by phone or face-to-face according to their preference.

Consent

At the assessment appointment, the principal investigator (RAH) discussed the information sheets with the participant and the parent/caregiver. Written assent and consent was obtained from each participant and the parent/caregiver individually, after any questions had been answered. If the parent/caregiver was not present at the appointment, RAH discussed the information sheet over the telephone and written consent was obtained prior to the clinical assessment. Written consent from the child was obtained at the assessment appointment.

Health questionnaire

At the study appointment, the mother of each participant was asked to complete a structured health questionnaire for the child and a structured questionnaire on her health during pregnancy and her smoking habits (Appendix 9). If the participant’s mother was not present at the appointment, the questionnaire was completed by telephone.
The health questionnaire recorded demographic (age, gender, SES) information, medical history and fluoride history (based on the suburbs lived in) for the first four years of participant’s life, family history of similar defects. The second part of the questionnaire recorded the mother’s age, employment status, education level and smoking habits as well as details of the pregnancy and birth (Appendix 9).

The information relied on parental recall of the information.

Clinical examination

The participants each received a complete oral examination in a dental chair with an overhead dental light and a dental mirror only.

On specific coded examination forms, the following was recorded by a trained dental assistant:

i. Teeth present
ii. Developmental enamel defects present
iii. Caries and restorative status of all teeth

Dentition status

i. Developmental defects of enamel (Appendix 7)

The modified developmental defects of enamel (DDE) index was used (World Health Organization, 1997, FDI Commission on Oral Health Research and Epidemiology, 1992). The status of the tooth surface was diagnosed on teeth cleaned and dried using gauze, and recorded on specific examination
form. Surfaces were inspected visually for defects and, if there was any doubt, areas that appeared to have hypoplastic pits were checked with a periodontal probe to confirm the diagnosis. Any gross plaque or food deposits were removed.

Enamel defects were classified into one of three types on the basis of their appearance. They varied in their extent, position on the tooth surface, and distribution within the dentition. Specific areas of concern in differentiating between enamel opacities and other defects in dental enamel were: (a) white spot demineralisation; and (b) white opaque cuspal and marginal ridges on premolar and molar teeth and, occasionally on incisal edges of lateral incisors (FDI Commission on Oral Health Research and Epidemiology, 1992).

Enamel hypomineralisation was defined as demarcated opacities that range in presentation from chalky white-opaque lesions with loss of translucency to yellow or brown lesions (Weerheijm et al., 2003).

Enamel hypoplasia was defined as a defect involving deficient enamel surfaces or the absence of enamel. Affected areas may be translucent or opaque. The borders between sound and hypoplastic enamel are smooth (Weerheijm et al., 2003).

Fluorotic lesions were defined as bilaterally symmetrical lesions with horizontal striations across the tooth surface. They vary in colour from white-opaque to brown and can appear as flecks, spots or corroded surfaces.
The codes and criteria are as follows:

Presence of the tooth (in column P):

1 = Present  
2 = Missing  
3 = Deciduous

DDE codes:

0 = Sound  
1 = Demarcated opacity  
2 = Diffused opacity  
3 = Hypoplasia  
4 = Other defects  
5 = Demarcated and diffuse opacities  
6 = Demarcated opacity and hypoplasia  
7 = Diffuse opacity and hypoplasia  
8 = All three conditions  
9 = Not recorded

Teeth surfaces were classified based on the classification described below.

A sound surface (0) displays no evidence of enamel defects.

A demarcated opacity (1) was defined as a demarcated defect that is in enamel of normal thickness with an intact surface. The translucency of enamel is variable in degree. The boundary between the adjacent normal enamel is distinct and clear. The colour varies from white, cream, yellow or brown.
A diffused opacity (2) was defined as a defect involving an alteration in the translucency of the enamel, variable in degree, and white in colour. The boundary between the adjacent normal enamel is not clear. The opacity can be linear or patchy or have a confluent contribution.

Hypoplasia (3) was defined as a defect involving the surface of the enamel associated with a localized reduction in the thickness of the enamel. It can occur in the form of: (a) pits-single or multiple, shallow or deep, scattered, or in rows arranged horizontally across the tooth surface; (b) grooves-single or multiple, narrow or wide (maximum 2mm); or (c) partial or complete absence of enamel over a considerable area of dentine. The affected enamel may be translucent or opaque.

The tooth surface with single abnormality of less than 1mm in diameter or if there is any doubt about the presence of abnormality was scored as sound (0).

Any abnormality that cannot be readily classified into one of the three basic types was scored as “other defects” (4).

If more than two-thirds of the tooth surface was heavily restored, covered with calculus, badly decayed or fractured was not examined and given the code (9).

A tooth was regarded as present once any part of it has penetrated the mucosa and any defect present on the erupted part of it was recorded. Unerupted surfaces or tooth were not examined and given the code (9).
ii. Dental caries status (Appendix 8)

The status of the tooth was diagnosed on teeth cleaned and dried with gauze, using a good light source and dental mirror; and recorded on specific examination form.

Presence of the tooth (in column P):

1 = Present  
2 = Absent  
3 = Deciduous  

Classification of the tooth surfaces:

0 = Sound  
1 = Decayed  
2 = Filled  
3 = Filled and decayed  
4 = Demineralised/Precavitated  
5 = Missing due to caries  
6 = Missing due to other reason  
7 = Unerupted  
8 = Not recorded  
9 = Fissure sealant

Teeth surfaces were classified based on the classification described below.

A sound surface (0) is one that displays no evidence of caries. This includes no or questionable changes in enamel translucency after drying with gauze; surfaces with developmental defects such as enamel hypomineralisation/hypoplasia, fluorosis, tooth wear (attrition, abrasion or
erosion) and extrinsic stains (Ismail et al., 2007, World Health Organization, 1997).

A decayed surface (1) was defined as any cavitation of the enamel and/or its extension into dentine.

A filled surface (2) was defined as one that had a restoration and included preventive resin restorations.

A filled and decayed surface (3) was defined as a restoration with secondary caries or a fissure sealant with visible caries around the margins.

Diagnosis of a demineralised/precavitated lesion (4) depends on the evaluation of its opacity and discoloration. The lesion was defined as the "the first visual change in enamel", which appears as either a whitish/yellowish opaque (chalky) dull surface (active) or a whitish/brownish/blackish smooth shiny surface (inactive). These lesions can be visible on wet surfaces or after prolonged air-drying (5 seconds). In the pits and fissures, these lesions are limited to the confines of the pits and fissures.

Teeth missing (extracted) due to extensive caries were coded as 5.

Teeth missing due to other reasons, such as those that are confirmed congenitally missing or extracted for orthodontic reasons, periodontal disease or trauma, were coded as 6.

Unerupted teeth were coded as 7. For the purposes of the clinical examination, all teeth were presumed present (no congenitally absent teeth was noted).

Tooth wear is defined as substantial tooth surface loss and encompasses the combined processes of erosion, attrition and abrasion.
iii. Clinical photographs

A Nikon D80 camera fitted with a Nikon macro lens (AF-S Micro Nikkor 105mm 1:2.8 G ED) and ring flash was used for the intraoral photographs of the participants. The aperture was set at f-32 with a shutter speed of 1/80 on manual exposure to allow sufficient exposure and depth of field. ISO was set at 100 to maximize the signal-to-noise ratio to avoid grainy pictures.

The lips and cheeks were retracted using plastic cheek retractors by the dental assistant. Intraoral photographic mirrors were used for occlusal, lingual or palatal and lateral views of the teeth. The mirrors were warmed before use to prevent condensation or fogging on the mirror surfaces, and participants were asked to breathe through their nose during the process.

The digital images were recorded on a Kingston SDHC memory card. The clinical photographs will be kept and used for future research.

Medical records

Detail of the child and mother’s health status during the perinatal and early postnatal period was recorded from the medical notes (Appendix 10).

Children’s medical records were used to obtain information on vascular pressure effect, APGAR score, any oxygen deprivation and breathing difficulties, were there any foetal distress, drugs used in neonatal period, birth weight or other problems so as to determine whether any problems occurred around the time of birth that may have affected the developing enamel.

Mothers’ medical records were used to obtain the duration of the labour, duration or length of engagement in the birth canal, mode of delivery
and gestational period, drugs given and mothers medical problem such as low or high blood pressure as to determine whether any problems occurred around the time of birth that may have affected the developing enamel.

Vouchers

At the end of the examination, parents/caregivers and participants were informed that they would receive a summary of the results at the conclusion of the study. Each child was given a $20.00 book voucher to thank him/her for their participation.

Investigator training

Prior to the commencement of the study, RAH was trained in the use of the developmental defect of enamel index and dental caries classification by experienced researchers (WMT). Examinations were carried out on seven randomly selected 6- to 12-year-old children who were not participants of the current study.

Analysis and presentation of the data

Management of the data

Coded examination forms were used for recording the data collection. Anonymised data were entered onto a Microsoft Excel spreadsheet.
Data analysis

The data were analysed using Statistical Package for the Social Sciences (SPSS) 19.0 and STATA version 10. Univariate and descriptive statistics (and computation of the various summated scale scores) were computed. Differences among means were tested for statistical significance using analysis of variance (ANOVA) or other nonparametric test if the data were not normally distributed (Mann-Whitney U-test where two groups were compared, and Kruskal-Wallis tests where there were more than two). Differences among proportions were examined using Chi-square tests. Conditional logistic regression was used to compare the two groups while taking individual matches into account.

The alpha level was set at 0.05.
Chapter IV. Results

Sociodemographic characteristics

Seventy-two children aged 6 to 12 years, who had been diagnosed with MIH comprised the case group and were invited to participate in the current study. Of these, 46 children (64.9%) and their parent/caregiver consented to participate and 43 (93.5%) of the 46 participants completed both the clinical assessment and health questionnaires. Six of the children’s medical records were not available.

For the control group, 3 (12.5%) of the 24 children volunteered by the case group, and 49 (94.2%) of the 52 children identified in the Bachelor of Oral Health Clinic at the School of Dentistry, participated in the study. Thirty-nine (70.9%) children and their mothers completed both the clinical assessment and health questionnaires. Six of the children’s medical records were not available.

Therefore, the total number of participants in this study was 101. This was made up of 46 (64.9%) from the case group and 55 (72.4%) from the control group. However, only 82 children completed both the clinical assessment and health questionnaires, and so all data presented subsequently pertain to 43 cases and 39 controls.

Overall, there were 40 females and 42 males (Table 4.1). There was no statistically significant difference in the gender or ethnic distribution of the case and control groups. The mean age of the participants was 9.2 years (sd, 0.1). Eighty-four percent of the participants were of European or other descent, and 15.9 percent were of Māori descent. A higher proportion of children from the case group were the first-born children (48.8%), in comparison to only 38 percent of children from the control group.
<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group Case</th>
<th>Group Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40 (48.8)</td>
<td>22 (51.2)</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td>Male</td>
<td>42 (51.2)</td>
<td>21 (28.8)</td>
<td>21 (53.8)</td>
</tr>
<tr>
<td><strong>Mean age (sd)</strong></td>
<td>9.2 (0.1)</td>
<td>9.2 (0.1)</td>
<td>9.2 (0.1)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>13 (15.9)</td>
<td>6 (14.0)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>European/other</td>
<td>69 (84.1)</td>
<td>37 (86.0)</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td><strong>Birth order</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-born child</td>
<td>36 (43.9)</td>
<td>21 (48.8)</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Second/other</td>
<td>46 (56.1)</td>
<td>22 (51.2)</td>
<td>24 (61.5)</td>
</tr>
</tbody>
</table>

*Table 4.1. Sociodemographic characteristics of participants by group (%)*
Part 1. Oral assessment

Developmental defects of enamel

Table 4.2 presents the prevalence of enamel defects in the case and control group by types of enamel defects. The prevalence of demarcated opacities, demarcated and diffuse opacities and demarcated opacity and hypoplasia were significantly higher in the case group than in the control group ($p < 0.05$). There were no other statistically significant differences but more participants in the case group had at least one tooth surface affected by diffuse opacities, hypoplasia and combination of two or more types of enamel defects (Table 4.2 and Table 4.4).

Data on the types of enamel defects in children diagnosed with MIH and children without MIH are presented in Table 4.3. The case reported significantly more demarcated opacities than the control group. However, diffuse opacities in both groups were similar. There were a higher number of surfaces affected by other types of enamel defects in the case group than in the control group.
Table 4.2. Number (%) of children with at least one surface of tooth affected by enamel defects, by group

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>Demarcated opacities</td>
<td>67 (66.3)</td>
<td>46 (100.0)</td>
</tr>
<tr>
<td>Diffuse opacities</td>
<td>69 (68.3)</td>
<td>35 (76.1)</td>
</tr>
<tr>
<td></td>
<td>3 (3.0)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Demarcated and diffuse opacities</td>
<td>46 (45.5)</td>
<td>42 (91.3)</td>
</tr>
<tr>
<td></td>
<td>11 (10.9)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>3 (3.0)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other defects</td>
<td>62 (61.4)</td>
<td>31 (67.4)</td>
</tr>
<tr>
<td></td>
<td>34 (61.8)</td>
<td>31 (56.4)</td>
</tr>
<tr>
<td>Other defects and hypoplasia</td>
<td>7 (6.9)</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>Hypoplasia and diffuse opacities</td>
<td>6 (5.9)</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>All three types of defect</td>
<td>6 (5.9)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Table 4.3. Mean (sd) number of teeth affected by types of enamel defects in children diagnosed with MIH and children without MIH, by group

<table>
<thead>
<tr>
<th>Demarcated opacities</th>
<th>All combined</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
</tr>
<tr>
<td></td>
<td>6.8 (8.0)</td>
<td>14.1 (6.1)a</td>
</tr>
<tr>
<td>Diffuse opacities</td>
<td>4.1 (8.1)</td>
<td>4.1 (5.0)</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>0.1 (0.4)</td>
<td>0.1 (0.6)</td>
</tr>
<tr>
<td>Other defects</td>
<td>1.6 (2.1)</td>
<td>1.9 (2.5)</td>
</tr>
<tr>
<td>Demarcated and diffuse opacities</td>
<td>2.7 (4.4)</td>
<td>5.7 (4.9)</td>
</tr>
<tr>
<td>Demarcated opacities and hypoplasia</td>
<td>0.3 (1.3)</td>
<td>0.6 (1.8)</td>
</tr>
<tr>
<td>Diffuse opacities and hypoplasia</td>
<td>0.2 (1.0)</td>
<td>0.4 (1.4)</td>
</tr>
<tr>
<td>All three types of defect</td>
<td>0.1 (0.4)</td>
<td>0.2 (0.6)</td>
</tr>
</tbody>
</table>

aP<0.05
Table 4.4. Mean (sd) number of surfaces affected by enamel defects

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Case</th>
<th>Group Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demarcated opacity including combinations</td>
<td>9.9 (11.6)</td>
<td>20.7 (9.1)</td>
<td>1.0 (1.6)</td>
</tr>
<tr>
<td>Diffuse opacity including combination</td>
<td>7.1 (9.9)</td>
<td>10.5 (8.5)</td>
<td>4.3 (10.5)</td>
</tr>
<tr>
<td>Hypoplastic defects including combination</td>
<td>0.1 (1.8)</td>
<td>1.4 (2.6)</td>
<td>0.1 (0.3)</td>
</tr>
</tbody>
</table>
Data on the prevalence and mean number of MIH-affected first permanent molars and permanent central incisors are presented in Table 4.5. There were no statistically significant differences between the females and males in the occurrence of MIH-affected first permanent molars. There were no statistically significant differences between maxillary and mandibular first permanent molars. The mean number of affected first permanent molars score was similar in females (mean 3.4, sd 0.1) and males (mean 3.6, sd 0.1). Females heed a higher number of affected mandibular lower central incisors than males as presented in Table 4.5.

Table 4.6 presents a crosstabulation between the numbers of MIH-affected first permanent molars and number of affected permanent central incisors. While there were no statistically significant differences, those with higher number of affected molars tended to have more affected incisors.
Table 4.5. Prevalence of MIH-affected first permanent molars and permanent central incisors by gender in the case group (percentages in brackets refer to the proportion of teeth affected)

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 22$</td>
<td>$n = 21$</td>
<td>$n = 43$</td>
</tr>
<tr>
<td>Tooth 16</td>
<td>18 (78.3)</td>
<td>21 (91.3)</td>
<td>39 (84.8)</td>
</tr>
<tr>
<td>Tooth 26</td>
<td>21 (91.3)</td>
<td>22 (95.7)</td>
<td>43 (93.5)</td>
</tr>
<tr>
<td>Tooth 36</td>
<td>18 (78.3)</td>
<td>20 (87.0)</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Tooth 46</td>
<td>20 (87.0)</td>
<td>19 (82.6)</td>
<td>39 (84.8)</td>
</tr>
<tr>
<td>Tooth 11</td>
<td>16 (69.6)</td>
<td>17 (73.9)</td>
<td>33 (71.7)</td>
</tr>
<tr>
<td>Tooth 21</td>
<td>17 (73.9)</td>
<td>18 (78.3)</td>
<td>35 (76.1)</td>
</tr>
<tr>
<td>Tooth 31</td>
<td>10 (43.5)</td>
<td>5 (21.7)</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Tooth 41</td>
<td>8 (34.8)</td>
<td>6 (26.1)</td>
<td>14 (30.4)</td>
</tr>
</tbody>
</table>
Table 4.6. Crosstabulation between numbers of MIH-affected first permanent molars and MIH-affected permanent central incisors among the case group (row percentages unless otherwise stated)

<table>
<thead>
<tr>
<th>Number of MIH-affected first permanent molars</th>
<th>Number of maxillary permanent central incisors with demarcated opacity</th>
<th>Number of mandibular permanent central incisors with demarcated opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>4</td>
<td>5 (15.6)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (13.0)</td>
<td>12 (26.1)</td>
</tr>
</tbody>
</table>
Dental caries

The distribution of number of permanent and deciduous teeth present is presented in Figure 4.1 and Figure 4.2. The mean number of permanent teeth present was 13.6 (sd, 5.6) and the mean number of deciduous teeth present was 9.3 (sd, 5.0).

Data on deciduous and permanent dentition caries experience by group are presented in Table 4.7. There was a statistically significance difference, with the case group having a higher overall caries experience in the deciduous and permanent dentitions than the control group (P<0.05). The prevalence of caries in the deciduous and permanent dentitions is presented in Figure 4.3 and Figure 4.4.
Table 4.7. Mean (sd) number of surfaces affected by caries in the permanent and primary dentitions, by group

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
</tr>
<tr>
<td>Mean DMFS</td>
<td>1.6 (2.9)</td>
<td>3.3 (3.6)</td>
</tr>
<tr>
<td>Mean dmfs</td>
<td>5.2 (8.8)</td>
<td>7.4 (10.1)</td>
</tr>
<tr>
<td>Mean number of teeth present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent teeth</td>
<td>13.6 (5.6)</td>
<td>14.0 (5.4)</td>
</tr>
<tr>
<td>Deciduous teeth</td>
<td>9.3 (5.0)</td>
<td>8.5 (4.7)</td>
</tr>
</tbody>
</table>

p<0.05
Figure 4.1. Distribution of number of permanent teeth present in both groups
Figure 4.2. Distribution of number of deciduous teeth present in both groups
Figure 4.3. Distribution of caries prevalence in deciduous dentition in both groups
Figure 4.4. Distribution of caries prevalence in permanent dentition in both groups
Part 2. Pre-, peri- and postnatal events assessment

Health questionnaires

Data on the distribution of pregnancy variables among mothers of children diagnosed with MIH and children without MIH are presented in Table 4.8. Mothers of the control participants appeared to have had more problems in pregnancy, although this was not statistically significant.

Table 4.9 presents the distribution of birth variables by group. The case group had a statistically significant higher number of premature births than the control. The mean gestational period was higher in the control group, although this was not statistically significant.

Table 4.10 presents the number of early childhood illnesses by group. There were no statistically significant differences between the case and control groups, although the case group appeared to have had higher experience of asthma, ear infection, tonsillitis, pneumonia, hand, foot and mouth disease (HFM), gastroenteritis and other gastrointestinal (GI) disturbances.

Data on general anaesthesia experience by group are presented in Table 4.11. A higher proportion of case group had had general anaesthesia experience, although this was not statistically significant.
Table 4.8. Distribution of pregnancy variables among mothers, by group (%)

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>Problems with pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (41.5)</td>
<td>14 (32.6)</td>
<td>20 (51.3)</td>
</tr>
<tr>
<td>No</td>
<td>48 (58.5)</td>
<td>29 (67.4)</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>Medication(s) during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (35.4)</td>
<td>15 (34.9)</td>
<td>14 (35.9)</td>
</tr>
<tr>
<td>No</td>
<td>53 (64.6)</td>
<td>28 (65.1)</td>
<td>25 (64.1)</td>
</tr>
</tbody>
</table>
Table 4.9. Distribution of birth variables, by group (%)

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group Case</th>
<th>Group Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td>66 (80.5)</td>
<td>30 (69.8)</td>
<td>36 (92.3)</td>
</tr>
<tr>
<td>Premature birth</td>
<td>16 (19.5)</td>
<td>13 (30.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Reported bleeding/bruising on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the face or head</td>
<td>17 (21.2)</td>
<td>8 (19.5)</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Mean gestational period (sd)</td>
<td>38.8 (2.5)</td>
<td>38.5 (3.0)</td>
<td>39.2 (1.7)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>71 (86.6)</td>
<td>36 (83.7)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>No</td>
<td>11 (13.4)</td>
<td>7 (16.3)</td>
<td>4 (10.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>p<0.05
Table 4.10. Experience (%) of early childhood illnesses, by group

<table>
<thead>
<tr>
<th>Illness</th>
<th>All combined</th>
<th>Group Case</th>
<th>Group Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>8 (9.8)</td>
<td>4 (9.3)</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>2 (2.4)</td>
<td>2 (4.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asthma</td>
<td>25 (30.5)</td>
<td>14 (32.6)</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (2.4)</td>
<td>2 (4.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>10 (12.2)</td>
<td>5 (11.6)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Rubeola (measles)</td>
<td>3 (3.7)</td>
<td>2 (4.7)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Rubella</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mumps</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Ringworm</td>
<td>4 (4.9)</td>
<td>1 (2.3)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>69 (84.1)</td>
<td>34 (79.1)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>Scabies</td>
<td>4 (4.9)</td>
<td>1 (2.3)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Glandular fever</td>
<td>1 (1.2)</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Slapped cheek infection</td>
<td>5 (6.1)</td>
<td>2 (4.7)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>11 (13.4)</td>
<td>5 (11.6)</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Salmonella</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Giardia</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>16 (19.5)</td>
<td>9 (20.9)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>HFM&lt;sup&gt;a&lt;/sup&gt; disease</td>
<td>7 (8.5)</td>
<td>7 (16.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Food allergies</td>
<td>8 (9.8)</td>
<td>3 (7.0)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Other GI&lt;sup&gt;b&lt;/sup&gt; disturbances</td>
<td>8 (9.8)</td>
<td>5 (11.6)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Congenital syndromes</td>
<td>2 (2.4)</td>
<td>1 (2.3)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>53 (64.6)</td>
<td>28 (65.1)</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>20 (24.4)</td>
<td>14 (32.6)</td>
<td>6 (15.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>HFM = Hand, foot and mouth  
<sup>b</sup>GI = Gastrointestinal
Table 4.11. General anaesthesia experience, by group (number of participants (%))

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group Case</th>
<th>Group Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have had GA</td>
<td>47 (57.3)</td>
<td>32 (74.4)</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Have had GA for dental procedure</td>
<td>19 (23.2)</td>
<td>15 (34.9)</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Have had GA for non-dental procedure</td>
<td>28 (34.1)</td>
<td>17 (39.5)</td>
<td>11 (28.2)</td>
</tr>
</tbody>
</table>

GA = general anaesthesia
Table 4.12 presents the family history of enamel defects, by group. Overall, there were no statistically significant differences in family history, although not statistically significant, the case group did have a higher number of siblings, parents, aunties, uncles, grandparents and cousins affected with enamel defects.

Sociodemographic data, mothers’ education level and smoking habits are presented by group in Table 4.13. There were no statistically significant differences in mothers’ age and ethnicity. Almost three-quarters of mothers in the case group had a lower education level and that a higher proportion of mothers in the case group smoked or was an ex-smoker.
Table 4.12. Family history of enamel defects among children with MIH and children without MIH (number of participants (%))

<table>
<thead>
<tr>
<th></th>
<th>All combined</th>
<th>Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling with enamel defects</td>
<td>13 (15.9)</td>
<td>11 (25.6)</td>
<td>2 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sibling</td>
<td>5 (6.1)</td>
<td>4 (9.3)</td>
<td>1 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sibling</td>
<td>6 (6.1)</td>
<td>5 (11.6)</td>
<td>1 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cousin with enamel defects</td>
<td>10 (12.2)</td>
<td>6 (14.0)</td>
<td>4 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female cousin</td>
<td>5 (6.1)</td>
<td>3 (7.0)</td>
<td>2 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male cousin</td>
<td>6 (7.3)</td>
<td>3 (7.0)</td>
<td>3 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cousin on mother’s side</td>
<td>11 (13.5)</td>
<td>6 (14.0)</td>
<td>5 (12.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father with enamel defects</td>
<td>3 (3.6)</td>
<td>3 (7.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aunties with enamel defects</td>
<td>2 (2.4)</td>
<td>2 (4.7)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncles with enamel defects</td>
<td>6 (7.4)</td>
<td>5 (11.7)</td>
<td>1 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal aunties or uncles</td>
<td>1 (1.2)</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal aunties or uncles</td>
<td>6 (7.3)</td>
<td>4 (10.3)</td>
<td>2 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandparents with enamel defects</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal grandparent(s)</td>
<td>2 (2.4)</td>
<td>2 (4.7)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal grandparent(s)</td>
<td>1 (1.2)</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All combined</td>
<td>Groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>3 (3.8)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to 39 years</td>
<td>41 (52.1)</td>
<td>21 (52.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to 50 years</td>
<td>33 (41.8)</td>
<td>18 (45.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>2 (2.6)</td>
<td>1 (2.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>9 (11.0)</td>
<td>4 (9.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European/others</td>
<td>73 (89.0)</td>
<td>39 (90.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or polytechnic</td>
<td>53 (66.2)</td>
<td>30 (73.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University graduate</td>
<td>27 (33.8)</td>
<td>11 (26.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>58 (70.7)</td>
<td>26 (60.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>10 (12.2)</td>
<td>6 (14.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>11 (13.4)</td>
<td>8 (18.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.13. Maternal age, ethnicity, education level and smoking habits, by group (number of participants (%))
Birth records

Data in Table 4.14 presents the distribution of birth circumstances by group. Although not statistically significant, a higher proportion of the case group had had oxygen deprivation and foetal distress. There were no statistically significant differences between groups in the mode of delivery and gestational period. More than 70 percent of the participants in the case group had a lower birth weight, but the difference was not statistically significant.

Table 4.15 presents data on mothers’ health status, analgesics received and length of labour by group. A higher proportion of mothers in the case group had received some form of analgesics and other medication, but these differences were not statistically significant. A higher proportion of mothers in the case group had received nitrous oxide during delivery, although this was not statistically significant. The mean time spent in labour was 6.1 hours for the case group and 5.4 hours for the control group.
Table 4.14. Birth circumstances, by group (number of participants (%))

<table>
<thead>
<tr>
<th>Vascular pressure effect on the face or head</th>
<th>All combined</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (6.8)</td>
<td>2 (5.0)</td>
<td>3 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Oxygen deprivation</td>
<td>6 (9.7)</td>
<td>4 (10.5)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>One or more signs of foetal distress</td>
<td>21 (31.8)</td>
<td>12 (32.4)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarian section</td>
<td>21 (28.0)</td>
<td>11 (26.8)</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>Normal vaginal delivery</td>
<td>48 (64.0)</td>
<td>26 (63.4)</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>Assisted vaginal delivery</td>
<td>6 (8.0)</td>
<td>4 (9.8)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Gestational period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 weeks</td>
<td>2 (2.7)</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>30- to 36-weeks</td>
<td>9 (12.2)</td>
<td>7 (17.5)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>37- to 40-weeks</td>
<td>51 (68.9)</td>
<td>26 (65.0)</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>&gt;40 weeks</td>
<td>12 (16.2)</td>
<td>5 (12.5)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500 grams</td>
<td>2 (2.9)</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1500 to 2499 grams</td>
<td>2 (2.9)</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2500 to 3499 grams</td>
<td>37 (52.9)</td>
<td>21 (52.5)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>3500 to 3999 grams</td>
<td>16 (22.9)</td>
<td>8 (20.0)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>&gt;4000 grams</td>
<td>13 (18.6)</td>
<td>7 (17.5)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Drugs received in neonatal period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>63 (94.0)</td>
<td>35 (94.6)</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Other medication</td>
<td>1 (1.5)</td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Antibiotic and other medication</td>
<td>2 (3.0)</td>
<td>1 (2.7)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>
Table 4.15. Mothers’ health status, analgesics and medication(s) received and length of labour, by group (%)

<table>
<thead>
<tr>
<th>Mother’s blood pressure</th>
<th>All combined</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>Within normal range</td>
<td>67 (87.0)</td>
<td>38 (90.5)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>10 (13.0)</td>
<td>4 (9.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs given to mothers during delivery</th>
</tr>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
</tr>
<tr>
<td>Pethidine</td>
</tr>
<tr>
<td>Antibiotic(s)</td>
</tr>
<tr>
<td>Other medications</td>
</tr>
<tr>
<td>Nitrous oxide and pethidine</td>
</tr>
<tr>
<td>Nitrous oxide and antibiotic(s)</td>
</tr>
<tr>
<td>Nitrous oxide, antibiotic(s) and other drug(s)</td>
</tr>
<tr>
<td>Epidural</td>
</tr>
<tr>
<td>Spinal</td>
</tr>
</tbody>
</table>

Mean hours spent in labour (sd)       | 5.8 (3.7)    | 6.1 (3.8)      | 5.4 (3.5) |
Figure 4.5. Distribution of length of labour time in both groups
Summary of results

There were no statistically significant differences in the gender or ethnic distribution of the case and control groups.

Children in the case group had a higher prevalence of demarcated opacities, demarcated and diffuse opacities, and demarcated opacity and hypoplasia children than in the control group (P<0.05).

There were no statistically significant differences between the females and males in the case group in the MIH-affected first permanent molars and permanent central incisors. There were no statistically differences in prevalences between the maxillary and mandibular first permanent molars in the case group.

Children in the case group had higher caries experience in both deciduous and permanent dentitions than those in the control group.

There were no statistically significant associations in MIH and early childhood illnesses. The case group appeared to have had higher experience of asthma, ear infection, tonsillitis, pneumonia, HFM disease, gastroenteritis and other GI disturbances, although this was not statistically significant.

In the association of MIH and birth circumstances, the number of premature birth was statistically significantly higher in the case group. A higher proportion of children in the case group had a lower birth weight than children in the control group (P<0.05).
Chapter V. Discussion

This thesis has focused on developmental disturbance in the enamel of permanent first molars and incisors, which is described as molar incisor hypomineralisation (MIH) with special emphasis on the clinical appearance of the teeth and a possible aetiology for MIH. The current study was designed to investigate and help identify factors from perinatal and postnatal time periods that could influence enamel development in the first permanent molars and incisors related to MIH.

The current study was designed as a matched case-control study with case participants recruited from the University of Otago Discipline of Paediatric Dentistry’s data records. The control group was frequency matched based on age, gender, and SES status. Case-control are commonly used to analytically assess the impact of a disease (MIH) or event, retrospectively. They are beneficial in assessing risk factors, allowing a smaller sample size. Matching based on age, gender, and SES allowed for these characteristics to be controlled in the measured variables.

Characteristics of the sample

The power of a case-control study lies in the similarities of the two groups. In the current study, the control sample was frequency matched for gender, age and SES. The slightly higher proportion of female participants (51.2%) in the sample does not reflect the gender allocation of children who were diagnosed with MIH. Previous studies in New Zealand on MIH prevalence showed gender and ethnicity are not modifying factor in the occurrence of developmental defects of enamel. The mean age of the children was 9.2 years (aged 6 to 12 years) for both the case and control groups.
Statistically there was no significant difference in the ethnic variation between the case and the control groups. The majority (84.1%) of the study participants identified themselves as being of European or other descent and 15.9 percent identified themselves as being of Māori descent. The study participants that identified themselves as being of Māori and European were grouped as being of Māori descent. The current study associates well with previous studies in New Zealand where there were no statistically significant association between MIH and ethnicity (Mahoney and Morrison, 2009, Mahoney and Morrison, 2011).

The clinical findings

Developmental defects of enamel

Criteria for diagnosing MIH proposed at the European meeting on MIH held in Athens in 2003 (Weerheijm et al., 2003) were used in identifying the case participants in the current study. The teeth were cleaned with gauze and were examined wet (not air dried) to ensure good reproducibility.

All (100.0%) of the children with MIH had at least one surface affected by demarcated opacities. MIH defects appeared to be higher in the first permanent molars than in the incisors (see Chapter IV, Table 4.5). In the first permanent molars, prevalence of MIH defects were similar but appeared to be higher in tooth 26 (93.5%), although this difference was not statistically significant. MIH defects were more common in the upper central incisors than in the lower central incisors. These findings were in agreement with previous studies that suggested that the upper first permanent molars are often affected than the lower first permanent molars (Leppäniemi et al., 2001, Suckling et al., 1985, Suckling and Pearce, 1984). Hypoplasia was seen in 6.5% and combination of demarcated opacities and hypoplasia was 19.6% in children with MIH.
Dental caries

The current study found a statistically significant difference in caries experience between the two groups. The case group had a higher overall caries experience in the deciduous and permanent dentitions than in the control group (p<0.05). However the filled component may have been over-estimated in the case group because most of their first permanent molars had been subjected to or were in need of extensive treatment despite a general good dental health with low caries activity. Also dental caries may be superimposed in areas of the tooth with post eruptive breakdown in children with MIH, and it was found difficult to classify the filled component as being due to caries or not. Despite some restorations being atypical. It was therefore decided to record them all as filled lesions.

Studies have suggested that a higher mean DMFS in children with MIH could be associated with post-eruptive breakdown of the fragile MIH-affected enamel and a relatively higher failure rate of restorations (Kotsanos et al., 2005, Jälevik and Klingberg, 2002, Chawla et al., 2008b). The defective enamel breaks down under direct occlusal loading, and it may also break down with shear loading transmitted through a restoration causing cohesive failure.

Association between MIH and pre-, peri- and postnatal events

The possible aetiologies in the occurrence of MIH have been widely reported in the literature (Alaluusua, 2010, Beentjes et al., 2002, Crombie et al., 2009, Fagrell, 2011, Kuscu et al., 2008, Laisi et al., 2009, Lygidakis et al., 2008, Muratbegovic et al., 2007, Weerheijm, 2004, Whatling and Fearne, 2008). It has been suggested that MIH defects in permanent teeth depend on several aetiologic factors responsible for its occurrence. However, the exact causative factors remained unclear. It has been suggested that from birth through the first years of life is the most critical period for first molar and
incisor tooth development. Disturbances during this period of life has been shown to be associated with MIH. Studies (Alaluusua, 2010, Crombie et al., 2009) have suggested a number of reasons have contributed to difficulties in identifying possible aetiological factors(s) in the occurrence of MIH (such as unclear diagnostic criteria for classification of demarcated opacities, parents being unable to recall details with sufficient accuracy of events occurring 8 to 10 years earlier, variations in quality and completeness of observations noted in children’s and mothers’ medical records, and small sample size). The indices that have been used to date have not clearly allowed for the unique clinical features of MIH enamel such as the range of colours, the occurrence of post eruptive breakdown, the presence of atypical restorations or the patterns of defects on the crown surfaces.

Prenatal period

Unlike some earlier studies, no associations were found in the current study between MIH and medication taken by mothers or medical problems during pregnancy. Interestingly, medical problems during pregnancy were found to be more common in mothers of children without MIH (51.3%) than in mothers whose children were diagnosed with MIH (32.6%) although, this difference was not statistically significant due to the small sample size. Other studies have reported that medical problems were found to be more common in mothers of MIH children than in mothers whose children did have MIH (Whatling and Fearne, 2008, Lygidakis et al., 2008).

Perinatal period

Higher number of mothers of the case participants were recorded to have received some form of analgesia and other drugs during delivery. Twenty-seven percent had received nitrous oxide and oxygen, pethidine (12.5%), antibiotic(s) (15.0%), other medications (10.0%) and combination of several medications (2.5%).
Although not statistically significant, participants who were diagnosed with MIH had a higher occurrence of medical problems related to birth (such as oxygen deprivation, had one or more signs of foetal distress, premature births, low birth weight (LBW) and more were born through assisted delivery, and higher number of mothers of MIH children received nitrous oxide, pethidine and antibiotics during delivery). A previous study reported 48 percent of children with MIH had a medical problem related to birth (van Amerongen and Kreulen, 1995). Other previous studies did not find any association between MIH and medical problems related to birth (Beentjes et al., 2002, Whatling and Fearne, 2008, Dietrich et al., 2003).

In the current study, low birth weight and low gestational age were found to be associated with MIH. Developmental defects of enamel have been previously reported in the literature to be linked in prematurely born children. Premature infants are likely to have low birth weight, and premature and low birth weight infants are more likely to require intubation and have health problems including disturbances in calcium metabolism, acid regulation and oxygenation than full-term infants. The current findings were in agreement with other studies that have reported that prematurely born children were to have greater prevalence of enamel defects in both the primary (Johnsen et al., 1984, Seow, 1997, Fearne et al., 1994, Aine, 2000 #2, Drummond et al., 1992) and permanent dentitions (Seow, 1996, Aine et al., 2000). If these are due to disturbances in the last trimester of pregnancy and the perinatal period then it might be expected that the most likely permanent teeth to be affected would be the first permanent molars and incisors. The association between LBW and enamel defects is widely reported in the literature (Norén, 1983, Seow, 1987, Lai et al., 1997, Rugg-Gunn et al., 1998, Aine et al., 2000, Lunardelli and Peres, 2006, Ferrini et al., 2008). Both previous studies on prematurely born children and the current study indicate that disturbances in oxygen concentration during perinatal period might be one of the factors to have an effect on the development of demarcated opacities.
Early childhood illnesses

In the current study, the experience of common childhood illnesses including asthma, gastroenteritis, HFM disease, other GI disturbances, ear infection and tonsillitis was found to be high in the case group than in the control group, although this was not statistically significantly different probably due to the small sample size. These findings were consistent with studies that suggested an association between MIH and early childhood illnesses (Whatling and Fearne, 2008, Lygidakis et al., 2008, Jälevik et al., 2001b, Beentjes et al., 2002).

A common symptom in infectious childhood illnesses is fever and the child may be treated with antibiotics and/or antiinflammatory drugs, therefore it is difficult to distinguish the role from that of the disease itself or its treatment. Common childhood illnesses like ear infection and tonsillitis are present for a short time and the minimum time period that is effective enough to affect ameloblast function is likely to depend on the sensitivity of ameloblasts to the harmful factor(s) and the strength of these factor(s). Currently, the minimum time period to disturb ameloblasts to cause MIH-type lesions is difficult to define. In an animal study in monkeys by Suga (Suga, 1989) it was demonstrated that hypomineralisation and hypoplasia of the tooth germs were found two weeks after the monkeys had a sudden unknown systemic disorder. The tooth germ in these monkeys were at the late secretory and/or the early maturation stages.

It is possible that there may be different types of MIH, and there may be a genetic predisposition associated with one or more of a range of systemic insults occurring simultaneously, at a susceptible stage in the development of specific teeth to cause MIH. Because the development of teeth is occurring over time, insults at different times may also cause different forms of this problem.
Difficulties encountered

Before making conclusions on the findings of this study, the limitations of the study design and the difficulties encountered during the study need to be considered.

Sample size

The sample size of the current study was determined by the response rate of the case participants. A 50 percent response rate was estimated based on a previous study on MIH in children (Mahoney and Morrison, 2009). The small sample size of the current study impacts on the statistical significance of the associations and increased the probability that the findings were due to chance (type II error).

Participants recruitment

Case group

In the current study, the case group comprised of children who had been previously been diagnosed with MIH. They were identified from clinical records in the School of Dentistry.

The moderate response rate in the current study could be explained by several factors including unavailability, inaccessibility, dental anxiety, SES, or mobility. Although the majority of the assessments were carried out during the school holidays and after school hours, unavailability of the parents/caregivers because of work commitments, and difficulty in attending the School of Dentistry may have significantly affected the participation rate.
Since the targeted population was aged 6 to 12 years, participation was significantly influenced by the parent/caregiver. Recruitment ceased when no more participants could be recruited from the original sample and the planned end point for the study was reached. Due to the limited time frame, recruitment ceased after two invitations and follow-up telephone calls. Additional case participants may have been recruited if the study spanned a longer time period or additional incentives were offered.

Control group

The control group was identified through the case participants volunteering three children “who were like them”. This led to identification on 24 children of whom 3 participated in the study. The discrepancy in having enough controls to invite arose primarily due to the case group declining to volunteer “friends”. This could be related to case participant’s anxiety regarding clinical assessment, with case participants viewing participation as unpleasant and not wanting to volunteer. Studies (Jälevik and Klingberg, 2002, William et al., 2006b) has suggested that dental fear and anxiety are more common in children with MIH. The low participation of the controls may have been because they perceived no real benefit in taking part especially when MIH is not really known about and probably not seen as a significant problem.

Since the aim of the study was to obtain an age-gender-SES matched control group, similar factors that affected participation rates in the case group might be attributable to the control group; unavailability, and inaccessibility. To increase the number of control participants, a frequency matched sample of children attending the Dental Therapy clinics at School of Dentistry who fulfilled the criteria and were scheduled to have their annual dental examinations in May and June 2012 were invited to participate. To encourage participation, assessments were carried out during school hours together with their annual dental examination. This eliminated the hurdle of accessibility. Interviews with mothers were carried out via the telephone or face-to-face
according to their preference and convenience. As some of the mothers were working full-time and could not be contacted even after several phone calls, the issue of availability could not be overcome for all children invited.

Clinical photographs

Since the targeted population was aged 6 to 12 years, taking clinical photographs in some of these young children was difficult. Unsuccessful clinical photographs were generally in cases where the children were dentally anxious, or were not able to breathe nasally (such as from common colds, thus creating moisture on the mirror).

Health questionnaire

In case-control studies investigating recalled information, recall and selection bias are common problems encountered. The information were obtained through questionnaires or interviews, which rely on individual memory and recollection of event(s). This can lead to inaccuracies. Information given relating to the problems during pregnancy, gestational period and the child’s first years of life is subject to memory lapses in the mothers, especially in mothers of older children.

Birth records

Information from the birth records of the mothers and babies, and past medical history obtained from the mothers themselves relied on variation in quality and detail noted in the medical records. The lack of reliability can lead to measurement error due to missing information in the records or variation in the detail recorded.
Measurement error

The reliability and validity of a study and its findings are determined by the representation of the study samples to the larger groups they are derived from (external validity), the consistency of the measurements (internal validity), the reliability and validity of the materials used (internal validity). The measures used to assess each component in the current study have been validated and tested in other studies with samples of similar demographics (see Chapter III, Section 1). A lack of reliability can lead to measurement error either due to item non-response, missing medical records or lack of investigator consistency in the use of the measures.

The use of a single, trained investigator (as in the current study) increases the consistency and decreases bias in the clinical measures used. Missing records and item non-response can have a significant impact on the reliability of the measurement. In the current study, the majority of the questionnaires were completed by the investigator before the clinical assessment or by telephone, significantly minimizing item non-response. However, as the completion of the questionnaires relied on mothers’ availability, three questionnaires from the case group and sixteen questionnaires from the control group were not completed.
Chapter VI. Conclusions and future research

Conclusions

1. The occurrence of MIH defects appeared to be higher in the first permanent molars than in the incisors. Prevalence of MIH defects was similar in the maxillary first permanent molars and mandibular first permanent molars, but MIH defects were found to be higher in tooth 26 (93.5%), although this difference was not statistically significant.

2. MIH defects were more common in the maxillary incisors than in the mandibular incisors.

3. Children with MIH were diagnosed with a higher overall caries experience in the deciduous and permanent dentitions than in the children without MIH.

4. Children diagnosed with MIH had more medical problems related to birth, such as oxygen deprivation, had one or more signs of foetal distress, premature births, low birth weight (LBW), and were born through assisted delivery. Mothers of children diagnosed with MIH had received more drugs such as nitrous oxide, pethidine and antibiotic(s) during delivery.

5. No associations were found between the occurrence of MIH and medication(s) taken by mothers during pregnancy or medical problems during pregnancy.

6. The current research highlights the difficulties faced in investigating the aetiology of developmental defects of enamel.
Future research

Regular dental check ups in children with repeated illnesses in the first years of life are important to detect any teeth defects early. Children with opacities on erupted first permanent molars and incisors should have careful monitoring during the mixed dentition period. Children who are diagnosed with MIH should be targeted for increased preventive measures and early restorative intervention to decrease their susceptibility to breakdown of the teeth and poorer oral health.

Pre-, peri- and postnatal problems appeared to be a risk factor for developing MIH-like defects, and this developmental time is worthy of further investigation. However, a substantial amount of work will be required to establish their role of the individual problems and to clarify the specific role of these in the aetiology of MIH. Larger number will be required to provide a stronger level of evidence. Based on the present knowledge of the onset and timing of MIH as well as possible aetiological factors, clearly defined clinical protocols and indices, including collection of comprehensive environmental and genetic information in long-term prospective epidemiological studies are required to identify the aetiology/aetiologies of this challenging disorder.
References


Appendices

List of Appendices

Appendix 1. Letter of ethical approval from Lower South Regional Ethics Committee (Ref LRS/10/11/057)

Appendix 2. Letter of approval from Southern District Health Board, Dunedin School of Medicine, Research Advisory Group (Project ID 00690)

Appendix 3. Approval from Ngāi Tahu Research Consultation Committee

Appendix 4. Information sheets for the case group

Appendix 5. Information sheets for the control group

Appendix 6. Consent/Assent forms

Appendix 7. Developmental defects of enamel clinical data recording form

Appendix 8. Dental caries index clinical data recording forms

Appendix 9. Questionnaires

Appendix 10. Birth and medical record forms

Appendix 11. EAPD MIH Index

Appendix 12. DDE Index
Appendix 1

Lower South Regional Ethics Committee
Ministry of Health
229 Moray Place
Dunedin
Phone: (03) 479 8562
Email: lowersuth_ethicommitee@mh.govt.nz

15 March 2011

Ms Rohaida Abdul Halim
School of Dentistry
University of Otago
PO Box 647
Dunedin 9054

Dear Rohaida -

Re: Ethics ref: LRS/10/11/057 (please quote in all correspondence)
Study title: Identification of factors in the natal and neonatal period influencing enamel development in the first permanent molar and incisor teeth
Investigators: Ms Rohaida Abdul Halim, Associate Professor Bernadette K Drummond, Professor W Murray Thomson

This study was given ethical approval by the Lower South Regional Ethics Committee on 15 March 2011. This approval is valid until 31 August 2012, provided that Annual Progress Reports are submitted (see below).

Access to ACC
For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
— the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

Annual Progress Reports and Final Reports
The first Annual Progress Report for this study is due to the Committee by 15 March 2012. The Annual Report Form that should be used is available at www.ethicscommittees.health.govt.nz. Please note that if you do not provide a progress report by this date, ethical approval may be withdrawn.
A Final Report is also required at the conclusion of the study. The Final Report Form is also available at www.ethicscommittees.health.govt.nz.

We wish you all the best with your study.

Yours sincerely

[e-signed]

Rohan Murphy
Administrator
Lower South Regional Ethics Committee
Email: lowersouth_ethicscommittee@moh.govt.nz
15 November 2011

Ms Rohaida Abdul Halim
School of Dentistry
University of Otago
PO Box 647
Dunedin 9054

Dear Ms Abdul Halim

Ethics ref: LRS/10/11/057 (please quote in all correspondence)
Study title: Identification of factors in the natal and neonatal period influencing enamel development in the first permanent molar and incisor teeth

Thank you for your letter, which we received on 3 November 2011, enclosing documentation relating to the above-named study. This documentation has been reviewed and approved by the Chairperson of the Lower South Regional Ethics Committee under delegated authority.

Approved Documents

- Undated letter signed by Rohaida Abdul Halim and Bernadette K Drummond advising of a protocol amendment to invite children from the Southern District Health Board School Dental Service to participate in the control group of the study.
- "You are invited" document - Version 2 dated September 2011.

Please do not hesitate to contact me should you have any queries.

Yours sincerely

[Signature]

Kirsten Forrest
Administrator
Lower South Ethics Committee
Appendix 2

Health Research Office
Dunedin School of Medicine and Southern District Health Board

5/04/2011

Dr. Roland Broadbent
Paediatrics & Child Health, DSM

Dear Roland

REF: Study on causes of tooth defects

I am writing on behalf of the combined Southern District Health Board and Dunedin School of Medicine, Research Advisory Group (RAG) to confirm that the project mentioned above has been granted approval to proceed.

According to my records:
This project is due to commence: 04/04/2011
It is due to be completed by: 31/08/2012

If you have any questions with regards to this project please contact me quoting the project ID shown above.

Yours sincerely

Ruth Sharpe
Clinical Research Advisor

CC Pip Stewart, Southern DHB
Romaha Abdul Halim, School of Dentistry
Appendix 3

NGAI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KY KAI TAHU

22/06/2010 - 18
Tuesday, 22 June 2010

Associate Professor Drummond
Oral Sciences
Dunedin

Tēnā koe Associate Professor Drummond

Title: Identification of factors in the prenatal and neonatal period influencing enamel development in the first permanent molars and incisors.

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 22 June 2010 to discuss your research proposition.

By way of introduction, this response from the Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum, it states "Ngāi Tahu acknowledges that the consultation process outlined in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago”. As such, this response is not “approval” or “mandate” for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology; they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee bases consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

As this study involves human participants, the Committee strongly encourage that ethnicity data be collected as part of the research project. That is the questions on self-identified ethnicity and descent, these questions are contained in the 2006 census.

As there is an intention to analyse the data by ethnicity, the Committee suggests including in the research team a researcher with expertise in analysing and interpreting data by ethnicity.

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Otago Incorporated
Kāti Huirapa Rūnanga ki Puketenuki
Te Rūnanga o Moanauki
NGĀI TAUH RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KE KAI TAUH

The Committee suggests dissemination of the findings to relevant Māori health organisations, for example the National Māori Organisation for Dental Health, Oranga Niho and to Associate Professor John Broughton, who is involved in Māori Dental Health, University of Otago.

We wish you every success in your research and the Committee also requests a copy of the research findings.

The Committee notes that this proposal is student research. In respect of the Policy for Research Consultation with Māori at the University of Otago, the policy is for University Staff research. Student research may also be considered, but the student’s supervisor should be the first named Principal Investigator.

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 22 June 2010 to 22 December 2011.

The recommendations and suggestions above are provided on your proposal submitted through the consultation website process. These recommendations and suggestions do not necessarily relate to ethical issues with the research, including methodology. Other committees may also provide feedback in these areas.

Nāhaku noa, nā

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Facilitator Research Māori
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Web: www.otago.ac.nz

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Či趔kou Incorporated
Kati Haupori i Whakatākiri ki Puketapu
Te Rūnanga o Moeraki
Appendix 4

Study of causes of tooth defects

Information sheet for mothers

Principal Investigator: Rohaida Abdul Halim
Graduate student (D Clin Dent in Paediatric Dentistry)

Supervisors: Associate Professor Bernadette K Drummond
Professor W Murray Thomson

Department of Oral Sciences
School of Dentistry
University of Otago
PO Box 647
Dunedin 9054
Tel: 03 479 3555
Introduction

You and your child are invited to take part in a study of the causes of a condition called Molar-Incisor Hypomineralisation (MIH). You can take as much time as you like to consider if your child and you are happy to participate in this study. To help you decide whether you/your child would like to take part in the study, please read this information sheet carefully. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss any aspect of the study. Please take time to read the following information carefully and discuss it with others if you wish. Taking part in this study is voluntary (your choice) and you/your child can decline to participate in the study. This will in no way affect your child's planned or continuing dental care at the School of Dentistry. We thank you for considering taking part in this study.

What is the study about?

This study is about a condition called Molar-Incisor Hypomineralisation (MIH), which means the enamel of the first molar teeth has not formed properly. This condition may present as white chalky spots, or yellow-brown areas on teeth, or rough pitted areas on teeth. It is not clear what causes this condition, but suggestions include early childhood illnesses or problems around the time of birth. This study will compare children who have MIH with children of the same age who do not have this problem.

The teeth with this problem are often very sensitive because of the thin and chipped enamel. The teeth are usually very difficult to fill because filling materials do not stick properly to the teeth.

Our study is looking at the possible causes of this condition in order to understand how the damage occurs. We hope with this knowledge, it may be possible to develop early prevention and better filling materials.

What is involved?

Should your child and you agree to take part in this study; the following steps will be taken:

1. You and your child will be asked to sign a consent form to participate in this study.
2. You will be asked for permission to review the birth records to check if there were any related problems during that period.
3. A dental examination to look at the health of your child's teeth, gums and mouth will be performed. At this examination, you will also be asked to complete a questionnaire about your health status during pregnancy, complications during delivery and your child's health during the first 4 years of life. This will take approximately one hour.
4. You will also be asked for consent for us to check the birth records for your child and to determine if there are any factors which may contribute to causing MIH.
5. The answers to the questionnaires will be recorded in a coded file which will only be available to the researchers. The records will be given a linked number and you and your child’s names will be kept separate from this so that no identifying data will be published in any form. The information we collect from you will be kept for 10 years after your child turns 15 years-of-age, after which the records will be destroyed. The results will be presented at dental meetings and published in scientific journals.

6. We shall send you a summary of the results at the end of the study. We shall also contact you if we discover any specific information about your child’s teeth that may help the diagnosis or his/her treatment.

Benefits, risks and safety

You will be advised if any problems with your child’s teeth, gums or mouth are found. The information that we obtain from this study will help us gain knowledge to develop appropriate early prevention and improved treatment for teeth that do not form properly.

Costs

There will be no fees charged for the dental examination. Dental treatment is NOT provided in this study. However, if you require a referral for dental treatment, this can be organized either within the School of Dentistry or at your own dentist. Your child will receive a $20 movie or petrol voucher for taking part.

Confidentiality

No material that could personally identify you or your child will be used in any reports of this study. The data collected will be stored securely so that only those directly involved in the research will have access to the records. At the end of the study, any raw data on which the results of the study depend will be retained in secure storage for 10 years after your child turns 15 years-of-age, as required by the HRC policy, after which it will be destroyed.

Participation

You and your child’s participation in this study are totally voluntary (you and your child’s choice). You and your child do not have to take part in this study, and if you choose not to take part, your child will receive any planned dental care as normal, and no future care or treatment will be affected. We would be grateful if you would be willing to participate in the study. I will contact you personally after a week and arrange for a suitable time for you to come for the dental examination if you agree. At this appointment I will answer any questions and you will and your child will be asked to sign consent forms. You are both free to withdraw from the study at any time, without having to give a reason.
General Information

1. If you need an interpreter for the study, the School of Dentistry will try to make one available - please circle the appropriate box on the consent form. If an interpreter cannot be found, you may be asked to bring your own. You may have a friend, family or whanau support to help you understand the inconveniences and/or benefits of this study and any other explanation you may require.

2. In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this study.

3. At the end of the study (in two years time) we will send you a summary of the results of the study. The results of the study will be available in the University of Otago Library and will be submitted for publication in dental journals. There is often a considerable delay between data collection and publication. Alternatively you can discuss the outcomes with the researcher.

4. If you wish, you may sign the part of the consent form which allows us to give information to your child’s dental therapist or dentist about any significant clinical factors that are discovered which could be of help in treating your child. We will confirm this again by a phone call.

5. This study has received approval from Lower South Regional Ethics Committee on 15th March 2011.

6. If you/your child have any queries or concerns regarding your child’s rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate:
   
   Telephone: (03) 479 0265
   Free phone: 0800 555 050
   Free fax: 0800 2 SUPPORT (0800 2787 7678)
   Email: advocacy@hdc.org.nz

Further Information

If you have any questions about the project, either now or in the future, please do not hesitate to contact:

Principal Investigator: Ms. Rohaida Abdul Halim
Supervisors: Associate Professor Bernadette Drummond
            Professor Murray Thomson
Department of Oral Sciences
School of Dentistry, University of Otago
Telephone Number: 03 479 3555
You are invited!

Study of causes of tooth defects

What is the study about and why we are doing it?
Your molar teeth at the back have some chalky spots on them. We want to find out why your teeth have these spots that can make them very sensitive to cold. If we can work out what causes this problem, we will be able to find ways to improve these teeth or find fillings that work better.

Would you like to take part?
If you would like to help us, you can come with your mum for us to look at your teeth and ask you some questions.

What will you need to do?
When you come to see us at the School of Dentistry, we will look into your mouth to check your teeth. We will also take some radiographs (x-rays) and photographs of your teeth if we don’t have them already. We shall also ask your mum some questions about your health when you were a baby.

You and your mum will be given a petrol voucher for helping us.

If you change your mind, there is no need to worry about it and that is fine with everybody. It is your decision whether to take part or not. We are happy to answer any questions you have.

Thank you for your help.

Researchers and their contact numbers:
Rohaida Halim (03) 479 3555
Bernadette Drummond (03) 479 7128
Appendix 5

Study of causes of tooth defects

Information sheet for mothers

Principal Investigator: Rohaida Abdul Halim
Graduate student (D Clin Dent in Paediatric Dentistry)
programme
Department of Oral Sciences
School of Dentistry
University of Otago
PO Box 647
Dunedin 9054
Tel: 03 479 3555

Supervisors
Associate Professor Bernadette K Drummond
Professor W Murray Thomson
Department of Oral Sciences
School of Dentistry
University of Otago
PO Box 647
Dunedin 9054
Introduction

You and your child are invited to take part in a study of the causes of a condition called Molar-Incisor Hypomineralisation (MIH), which causes the first adult molar teeth to be soft and chalky. You can take as much time as you like to consider if your child and you are happy to participate in this study. This time frame does not affect any planned treatment for your child.

Your child has been chosen from the School Dental Service list. To help you decide whether you/your child would like to take part in the study, please read this information sheet carefully. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss any aspect of the study. Please take time to read the following information carefully and discuss it with others if you wish. Taking part in this study is voluntary (your choice) and you/your child can decline to participate in the study, and this will in no way affect your child's continuing dental care at the School of Dentistry.

We thank you for considering taking part in this study.

What is the study about?

This study is about a condition called Molar-Incisor Hypomineralisation (MIH), which means the enamel of the first molar teeth has not formed properly. This condition may present as white chalky spots, or yellow-brown areas on teeth, or rough pitted areas on teeth. It is not clear what causes this condition, but the causes may be from early childhood illnesses or problems around the time of birth. This study will compare children who have MIH with children of the same age who do not have this problem.

The teeth with this problem are often very sensitive because of the thin and chipped enamel. The teeth are usually very difficult to fill because filling materials do not stick properly to the teeth.

Our study is looking at the causes of this condition in order to understand how the damage occurs. We hope with this knowledge, it may be possible to develop early prevention and better filling materials.

The study will assess your child’s dental health and you will be given questionnaire about your health status during pregnancy and complications during delivery. You will also be asked for permission to review the birth records to check if there were any related problems during that period. There will be a questionnaire about your child’s health during the first four years of life. Many of the answers may be in your child’s Plunket book. All children and parents who participate in this study will receive a book or petrol voucher.
What is involved?

Should your child and you agree to take part in this study; the following steps will be taken:

7. You will be asked to sign a consent form on behalf of you and your child to participate in this study. Your child will have a form to sign as well.
8. A dental examination to look at the health of your child's teeth, gums and mouth will be performed.
9. You will also be asked to about your health status during pregnancy, complications during delivery and your child's health during the first 4 years of life. This will be done through telephone interview and will take approximately 30 minutes.
10. You will also be asked for consent for us to check the birth records for your child and to determine if there are any factors which may contribute to causing MIH.
11. The answers to the questionnaires will be recorded in a coded file which will only be available to the researchers. The records will be given a linked number and you and your child’s names will be kept separate from this so that no identifying data will be published in any form. The information we collect from you will be kept for 10 years after your child turns 15 years-of-age, after which the records will be destroyed. The results will be presented at dental meetings and published in scientific journals.
12. We shall send you a summary of the results at the end of the study. We shall also contact you if we discover any specific information about your child’s teeth that may help the diagnosis or his/her treatment.

Benefits, risks and safety

You will be advised if any problems with your child's teeth, gums or mouth are found. The information that we obtain from this study will help us gain knowledge whether we can develop appropriate early prevention and improved treatment for teeth that do not form properly.

Costs

There will be no fees charged for the dental examination. Dental treatment is NOT provided in this study. However, if you require referral for dental treatment within the School of Dentistry or your own dentist, this is generally covered by the public dental system for children. Your child will receive a $20 book voucher for taking part.

Confidentiality

No material that could personally identify you or your child will be used in any reports of this study. The data collected will be stored securely so that only those directly involved in the research will have access to the records. At the end
of the studies, any raw data on which the results of the study depend will be retained in secure storage for 10 years after your child turns 15 years-of-age, as required by the HRC policy, after which it will be destroyed.

Participation

You and your child's participation in this study are totally voluntary (you and your child's choice). You and your child do not have to take part in this study, and if you choose not to take part, your child will receive any planned dental care as normal, and no future care or treatment will be affected.

We would be grateful if you would be willing to participate in the study. I will contact you personally after a week and arrange for a suitable time for you to come for the dental examination if you agree. At this appointment I will answer any questions and you will and your child will be asked to sign consent forms.

You are both free to withdraw from the study at any time, without having to give a reason and this will in no way affect yourchild's future dental care.

General Information

7. If you need an interpreter for the study, the School of Dentistry will try to make one available - please circle the appropriate box on the consent form. If an interpreter cannot be found, you may be asked to bring your own. You may have a friend, family or whanau support to help you understand the inconveniences and/or benefits of this study and any other explanation you may require.

8. In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this study.

9. At the end of the study (in two years time) we will send you a summary of the results of the study. The results of the study will be available in the University of Otago Library and will be submitted for publication in dental journals. There is often a considerable delay between data collection and publication. Alternatively you can discuss the outcomes with the researcher.

10. If you wish, you may sign the part of the consent form which allows us to give information to your child's dental therapist or dentist about any significant clinical factors that are discovered which could be of help in treating your child. We will confirm this again by a phone call.

11. This study has received approval from Lower South Regional Ethics Committee on 15th March 2011.
12. If you/your child have any queries or concerns regarding your child’s rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate:

   Telephone: (03) 479 0265
   Free phone: 0800 555 050
   Free fax: 0800 2 SUPPORT (0800 2787 7678)
   Email: advocacy@hdc.org.nz

Further Information

If you have any questions about the project, either now or in the future, please do not hesitate to contact:

Principal Investigator: Ms. Rohaida Abdul Halim
Supervisors: Associate Professor Bernadette Drummond
            Professor Murray Thomson
Department of Oral Sciences
School of Dentistry, University of Otago
Telephone Number: 03 479 3555
Study of causes of tooth defects

What is the study about and why we are doing it?

We want to find out why some teeth have some chalky spots on them that can make them very sensitive to cold. If we can work out what causes this problem, we will be able to find ways to improve these teeth or find fillings that work better.

Would you like to take part?

You were chosen from the School Dental Service list.

If you would like to help us, we will go to your school clinic to look at your teeth and ask you some questions.

What will you need to do?

We will look into your mouth to check your teeth. We shall also ask your mum to answer some questions about your health when you were a baby.

You will be given book or petrol voucher for helping us.

If you change your mind, there is no need to worry about it and that is fine with everybody. It is your decision whether to take part or not.

We are happy to answer any questions you have.

Thank you for your help.

Researchers and their contact numbers:

Rohaida Halim (03) 479 3555
Bernadette Drummond (03) 479 7128
Consent Form For Mothers

Study of causes of tooth defects.

Request for an interpreter

<table>
<thead>
<tr>
<th>Language</th>
<th>Translation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au I tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gardreva me dua e vakadewa vosa vei au</td>
<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean</td>
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<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Samoan</td>
<td>Out e mana’o ia i ai se fa’ amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
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<tr>
<td>Tokelaun</td>
<td>Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahefika</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
</tbody>
</table>
I have read the Information Sheet for participants concerning this study and understand what the study is about. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given. I also have had the opportunity to use whanau support or a friend to help me ask questions and understand the study. I understand that I am free to request further information at any stage.

My child was given full information about the research in a form that he or she could readily understand.

My child was given the opportunity to ask questions and to have those questions answered to my child's satisfaction.

I believe that ________________________ (participant’s name) would have chosen and consented to participate in this study if he/she had been able to understand the information that I’ve received and understood.

I understand that taking part in this study is voluntary (me and my child's choice) and that my child or I can decline participation and that I may ask for the information to be withdrawn at any time and that this will in no way affect my child’s planned and future dental care.

I understand that my and my child’s participation in this study is confidential and that no material which could identify me or him/her will be used in any reports on this study.

I understand that my data and my child’s data pertaining to my child’s participation in this project may be retained by the researchers for 5 years for continuous research. I understand any raw data on which the results of the study depend will be retained in secure storage for 10 years after my child turns 16. After this it will be destroyed. I also understand that my child has the right to withdraw consent to the continued use or retention of personally identifiable health research data once he or she attains the age of 16.

I know that the results of this project may be published but my and my child's anonymity will be preserved.

I also have had the time to consider whether to take part.

I know who to contact if I have any question about the study.

This study has been given ethical approval by the Lower South Regional Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedure.
1. I would like the principle researcher to discuss the outcomes of the study with me. Yes / No

2. I wish to receive a copy of the results. Yes / No

3. I wish my child to be referred to his/her dentist for further dental treatment. Yes / No

   I am aware that this treatment may or may not be covered and that I will need to check this with the dentist.

   If Yes, please provide the contact details of your child's dentist
   a. Name: ......................................................
   b. Address: ...................................................
      ..........................................................

4. I wish my child to be referred to the School of Dentistry for further dental treatment. Yes / No

   I am aware that treatment would be covered under contract with the DHB.

5. I agree and believe my child would agree to his/her dentist or doctor being informed of relevant clinical information. Yes / No

6. I consent to my records concerning my health status during pregnancy, complications during the birth of my child and my child's health during the first four years of life being reviewed. Yes / No

I __________________________________________ hereby consent to my information pertaining to the birth of my child being included in the study.

I __________________________________________ hereby consent to my child __________________________________________ taking part in this study.

Date:

Signature:

Address for results: ______________________________________________
   __________________________________________
   __________________________________________
Name of researchers:

1. Ms Rohaida Abdul Halim (Tel: 03 479 3555)
2. Associate Professor Bernadette Drummond (Tel: 03 479 7128)
3. Professor Murray Thomson (Tel: 03 479 7116)

Project explained by Ms Rohaida Abdul Halim, principal investigator.

Signature :________________________
Date :________________________
Study of causes of tooth defects

Consent form for children:

I have read and I understand the information sheet dated 15\textsuperscript{th} March 2011 for children taking part in the study looking at what causes tooth defects (chalky teeth).

I have had the chance to ask questions about this study. I am happy with the answers I have been given.

I have had the opportunity to use parental (mum or dad) support, whānau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is voluntary (my choice), and that I may pull out from the study at any time, and this will not change my care at the Dental School.

I understand that taking part in this study is private and no material that could identify me will be used in any reports on this study.

I know who to contact if I have any questions about the study.

There may be a significant delay in your participation in the data collection and the publication of the results.
I wish to receive a copy of the results.  
Yes  No

I agree to my doctor or dentist being given information about my teeth from the study, if needed.  
Yes  No

I ____________________________ (full name) agree to take part in this study.

Signature  : ____________________________

Date  : ____________________________

Name of researchers:

Ms Rohaida Abdul Halim  (Tel: 03 479 3555)
Associate Professor Bernadette Drummond  (Tel: 03 479 7128)
Professor Murray Thomson  (Tel: 03 479 7116)
## Appendix 7. DDE examination form

<table>
<thead>
<tr>
<th>ID No.</th>
<th>Examiner</th>
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</thead>
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### First quadrant

**(upper right)**

**For column P:**

- **Present** = 1
- **Missing** = 2
- **Deciduous** = 3

**DDE codes**

- 0 = sound
- 1 = demarcated opacity
- 3 = hypoplasia
- 4 = other defects
- 5 = demarcated and diffuse opacities
- 6 = demarcated opacity and hypoplasia
- 7 = diffuse opacity and hypoplasia
- 8 = all three conditions
- 9 = not recorded

<table>
<thead>
<tr>
<th>Tooth</th>
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### Second quadrant

**(upper left)**

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### Third quadrant (Lower left)

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<th>B</th>
<th>D</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For column P:</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Present  = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing  = 2</td>
<td></td>
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<td>Deciduous = 3</td>
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<td></td>
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</table>

**DDE codes**

- 0 = sound
- 1 = demarcated opacity
- 2 = diffuse opacity
- 3 = hypoplasia
- 4 = other
- 5 = demarcated and diffuse opacities
- 6 = demarcated opacity and hypoplasia
- 7 = diffuse opacity and hypoplasia
- 8 = all three conditions
- 9 = not recorded

### Fourth quadrant (Lower right)

<table>
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<tr>
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</table>
### Appendix 8. Dental caries examination form

**First quadrant**

(upper right)

For column P:

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<tr>
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<th>P</th>
<th>O</th>
<th>M</th>
<th>B</th>
<th>D</th>
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Surface status codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Sound</td>
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<tr>
<td>1</td>
<td>Decayed</td>
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<td>2</td>
<td>Filled</td>
</tr>
<tr>
<td>3</td>
<td>Filled and decayed</td>
</tr>
<tr>
<td>4</td>
<td>Demineralised/precavitated</td>
</tr>
<tr>
<td>5</td>
<td>Missing due to caries</td>
</tr>
<tr>
<td>6</td>
<td>Missing other reason</td>
</tr>
<tr>
<td>7</td>
<td>Unerupted</td>
</tr>
<tr>
<td>8</td>
<td>Not recorded</td>
</tr>
<tr>
<td>9</td>
<td>Fissure sealant</td>
</tr>
</tbody>
</table>

**Second quadrant**

(upper left)

<table>
<thead>
<tr>
<th>Tooth</th>
<th>P</th>
<th>O</th>
<th>M</th>
<th>B</th>
<th>D</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td></td>
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<td>27</td>
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</tr>
</tbody>
</table>
### Third quadrant

(Lower left)

**For column P:**
- Present = 1
- Missing = 2
- Deciduous = 3

**Surface status codes**
- 0 = sound
- 1 = decayed
- 2 = filled
- 3 = filled and decayed
- 4 = demineralised/precavitated
- 5 = missing due to caries
- 6 = missing other reason
- 7 = unerupted
- 9 = fissure sealant

<table>
<thead>
<tr>
<th>Tooth</th>
<th>P</th>
<th>O</th>
<th>M</th>
<th>B</th>
<th>D</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td></td>
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<td>36</td>
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<td>32</td>
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<td>31</td>
<td></td>
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</tr>
</tbody>
</table>

### Fourth quadrant

(lower right)

<table>
<thead>
<tr>
<th>Tooth</th>
<th>P</th>
<th>O</th>
<th>M</th>
<th>B</th>
<th>D</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
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<td>43</td>
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<td>46</td>
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<td>47</td>
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</tr>
</tbody>
</table>
Appendix 9

Study of causes of dental enamel defects.
Structured Questionnaire on General Health and Family History

Part A: General Questionnaire (child’s). Please tick or fill where space is provided.

1. Gender: Male ( )
   Female ( )

2. DOB: ________________

3. Ethnicity:
   New Zealand European ( )
   Māori ( )
   Samoan ( )
   Cook Island Maori ( )
   Tongan ( )
   Niuean ( )
   Chinese ( )
   Indian ( )
   Other such as Dutch, Japanese, Tokelauan. Please state ____________________

4. Does he/she have any siblings?
   Yes ( )
   No ( )

If “Yes”, how many and what is his/her place in family

__________________________________________________________
__________________________________________________________
I) Medical History:

A) Immunisation

1. Are your child’s immunisations up to date?
   Yes ( )
   No ( )
   If “No”, which immunisations has he/she missed?

_________________________________________
_________________________________________

B) Pregnancy and delivery:

1. Did you have any problems during pregnancy?
   Yes ( )
   No ( )
   Don’t know ( )

2. Were you taking any medications during pregnancy?
   Yes ( )
   No ( )
   Don’t know ( )
   If “Yes”, can you remember what they were?

______________________________________________________________________
______________________________________________________________________

3. Was he/she delivered?
   Full term ( )
   Prematurely ( )
   If prematurely, after how many weeks of pregnancy was he/she delivered?

______________________________________________________________________

4. Do you recall if your child had any bleeding or bruising on his/her head or face after being born?

______________________________________________________________________
______________________________________________________________________

5. Do you have a photograph of your child’s face in the first 1-2 days of life?

______________________________________________________________________
______________________________________________________________________
C) Breastfeeding:

1. Was your child breast fed?
   - Yes ( ) exclusive
   - Yes ( ) mixed
   - No ( )

   If "Yes", for how long? (or at what age was your child weaned?)
   ________________________________________________________________
   ________________________________________________________________

2. While breast feeding – were you taking any medications?
   - Yes ( )
   - No ( )

   If "Yes", what type of medication did you receive?
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________

D) Fluoride History:

1. Where (city/town) was your child born?
   ________________________________________________________________

   If bottle feeding, did you make up the formula with tap water?
   - Yes ( )
   - No ( )

2. Fluoride exposure

<table>
<thead>
<tr>
<th>Year</th>
<th>Town (lived)</th>
<th>Fluoride tablets &amp; duration</th>
<th>Toothpaste: Please state</th>
<th>Others: Please state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
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<tr>
<td>Year 3</td>
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<tr>
<td>Year 4</td>
<td></td>
<td></td>
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</tbody>
</table>
E) Childhood illnesses

1) Has your child suffered from any of the following diseases? Can you remember in which year of his/her life? And how severe it was?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
<th>Immunised</th>
<th>Which Year of life?</th>
<th>How severe was it?</th>
<th>What type of treatment or drugs did he/she receive for this condition?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whooping Cough</td>
<td></td>
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</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
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</tr>
<tr>
<td>Bronchiolitis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Rubella (Regular measles)</td>
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<tr>
<td>Rubella (German measles)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
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</tr>
<tr>
<td>Meningitis</td>
<td></td>
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</tr>
<tr>
<td>Ringworm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chicken pox</td>
<td></td>
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</tr>
<tr>
<td>Condition</td>
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<tr>
<td>Scabies</td>
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<tr>
<td>Glandular Fever</td>
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<tr>
<td>Slapped Cheek Infection</td>
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<tr>
<td>Impetigo (School Sores)</td>
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<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Giardia</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hand, Foot &amp; Mouth Disease</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
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</tr>
<tr>
<td>Hepatitis C</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Food Allergies or Intolerances</td>
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<td></td>
</tr>
<tr>
<td>(what type?)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disturbance</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
2. Has your child had a general anaesthetic?
   Yes ( )
   No ( )
If “Yes” when (date) was it?
___________________________________________________________________________
And what was it for?
_____________________________________________________________________________________
_____________________________________________________________________________________
_____________________________________________________________________________________

II) Family History:

i) Other than food allergies

ii) Congenital Diseases or Syndromes:

iii) Others:
   i-Ear infection
   ii-Tonsilitis
1. Does or did any of your child’s brothers or sisters suffer from the same or similar dental condition?
   - Yes (  )
   - No (  )
   - N/A (  )
   - Don’t know (  )

   If “Yes”, who?
   - Male (  )
   - Female (  )

2. Does or did any of your child’s cousins suffer from the same or similar dental problem?
   - Yes (  )
   - No (  )
   - Don’t know (  )

   If “Yes”, who?
   - Male (  )
   - Female (  )
   - Mother’s side (  )
   - Father’s side (  )

3. Does or did any of the child’s parents suffer from the same or similar dental problem?
   - Yes (  )
   - No (  )
   - Don’t know (  )

   If “Yes”, who?
   - Mother (  )
   - Father (  )

4. Does or did any of the child’s uncles or aunts suffer from the same or similar dental problem?
   - Yes (  )
   - No (  )
   - Don’t know (  )

   If “Yes”, who?
   - Uncle (  )
   - Aunt (  )
   - Mother’s side (  )
   - Father’s side (  )

5. Does or did any of the child’s grandparents suffer from the same or similar dental problem?
Yes   ( )
No    ( )
Don't know ( )

If “Yes”, who?
Male    ( )
Female   ( )
Mother’s side ( )
Father’s side ( )

6. Which school does your child attend?

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

6
164
Part B: General Questionnaire (Mother’s). Please tick or fill where space is provided.

1. Age: _______ years

2. Ethnicity:
   - New Zealand European ( )
   - Māori ( )
   - Samoan ( )
   - Cook Island Maori ( )
   - Tongan ( )
   - Niuean ( )
   - Chinese ( )
   - Indian ( )
   - Other such as Dutch, Japanese, Tokelauan. Please state __________________________

3. What is your employment status?
   - Full-time employed _________ ( )
   - Part-time employed _________ ( )
   - Self-employed _________ ( )
   - Unemployed ( )
   - Retired ( )
   - Housewife ( )

4. What is your partner’s employment status?
   - Full-time employed _________ ( )
   - Part-time employed _________ ( )
   - Self-employed _________ ( )
   - Unemployed ( )
   - Retired ( )

5. What is your highest level of education (degree obtained)?
   - High school ( )
   - Bachelor’s Degree ( )
   - Masters/PhD ( )
   - None ( )

6. Do you smoke?
   - Yes, still smoking ( )
   - Ex-smoker ( )
   - No, never smoked ( )

Thank you for answering all the questions. If you wish, a copy of the results of this study will be sent to you as soon as we get them. This, however, will probably take a couple of years. Do you have any questions for me? Would you like to have my contact details?
## Appendix 10

### Birth Record Information Data

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<thead>
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<th>ID No.</th>
<th></th>
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### Child

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<th>Yes</th>
<th>No</th>
<th>Notes</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td></td>
<td></td>
<td>Vascular pressure effects- capillary bleeding at birth time in the:-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1 face</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2 conjunctiva</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3 meningitis</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>Apgar scores:-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1 at 1 minute</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2 at 5 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.3 at 10 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.4 at 15 minutes</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>Oxygen deprivation/apnoea/hypoxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.1 Respiration/breathing established</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.2 Suction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3 Resuscitation/O₂</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>Mode of delivery: normal delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.1 Assisted delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.1.1 Forceps</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.1.2 Vacuum</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>4.2 Caesarian section (C-section)</td>
</tr>
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<td>4.2.1 Emergency C-section</td>
</tr>
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<td></td>
<td>4.2.2 Planned C-section</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>Birth weight</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>Drugs in neonatal period</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>Foetal distress</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>Others</td>
</tr>
</tbody>
</table>
### Mother

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.1 High blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2 Low blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Drugs given (including N₂O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Length of labour</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1 1&lt;sup&gt;st&lt;/sup&gt; stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2 2&lt;sup&gt;nd&lt;/sup&gt; stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.3 Membrane rupture before delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.4 Total time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Length of time baby’s head engaged in the birth canal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Epidural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Spinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>General anaesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Appendix 11**

**EAPD MIH Index**

EAPD definitions of the judgement criteria used in diagnosing MIH (Weerheijm et al., 2003)

<table>
<thead>
<tr>
<th>Demarcated opacities</th>
<th>A demarcated defect involving an alteration in the translucency of the enamel, variable in degree. The defective enamel is of normal thickness with a smooth surface and can be white, yellow or brown in colour.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-eruptive breakdown</td>
<td>A defect that indicates deficiency of the surface enamel after tooth eruption. The loss is often associated with a pre-existing demarcated opacity.</td>
</tr>
<tr>
<td>Atypical restoration</td>
<td>The size and shape of restorations are not conforming to the temporary caries picture. In most cases in molars there will be restorations extended to the buccal or palatal smooth surface. At the border of the restorations frequently an opacity can be noticed. In incisors a buccal restoration can be noticed not related to trauma. In cases of a large caries lesion with demarcated opacities at the border of the cavity or on the non caries surfaces, these teeth should be judged as MIH.</td>
</tr>
<tr>
<td>Extracted molar due to MIH</td>
<td>Absence of first permanent molar should be related to the other teeth of the dentition. Suspected for extraction due to MIH are: opacities or atypical restorations in the other first permanent molars combined with absence of a first permanent molar. Also the absence of first permanent molars in a sound dentition in combination with demarcated opacities on the incisors is suspected for MIH. It is not likely that incisors will be extracted due to MIH.</td>
</tr>
</tbody>
</table>
Appendix 12

DDE Index (World Health Organization, 1997)

Plate 2. Examples of coding of enamel opacities and hypoplasia
A: upper right first incisor—normal (code 0), lower left second incisor—demarcated opacity (code 1); B: upper right first incisor—demarcated opacity (code 1), upper left first incisor—demarcated opacity and hypoplasia (code 6); C: upper right first incisor—diffuse opacity (code 2), upper left first incisor—demarcated and diffuse opacities (code 5); D: upper first incisors—diffuse opacity (code 2); E: upper first incisors—diffuse opacity
(code 2); F: upper first incisors—diffuse opacity (code 2); G: upper first incisors—diffuse opacity (code 2); H: upper first incisors—diffuse opacity (code 2); I: upper right canine and first premolar—diffuse opacity and hypoplasia (code 7); J: upper left second incisor—diffuse opacity and hypoplasia (code 7); K: upper first incisors—hypoplasia (code 3); L: upper left second incisor—hypoplasia (code 3). (Source: reference 2. Used by permission.)